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JULY, 1950

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PROCEEDINGS
OF THE
CHEMICAL SOCIETY.

Minutes of a
SCIENTIFIC MEETING
held at Burlington House, London, W.1, on June 1st, 1950, at 7.15 p.m.

The President, PROFESSOR E. K. RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair.

The President welcomed Professor L. Ruzicka (Honorary Fellow), Professor and Mrs. L. F. Fieser, Dr. K. Miescher, Professor A. Plattner, Professor B. Riegel, and Dr. A. Wettstein, who were present.

MINUTES.

The Minutes of the Scientific Meeting held at the Royal Institution on May 4th were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: J. F. Bunnett, H. A. C. McKay, E. F. P. Harris, W. Hudson, H. Williams, H. G. Suggate, J. S. Coe, S. Siddappa, D. J. Cole, M. H. Jones.

SCIENTIFIC COMMUNICATIONS.

The President called upon Professor C. K. Ingold to read a summary of his papers entitled "Nitration and Nitrating Agents." A discussion followed, and Professor L. F. Fieser, on behalf of the visitors from overseas, expressed his appreciation in being able to attend the meeting.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
Harold Mennell (Manchester)	Sept. 17th, 1942.	Apr. 22nd, 1950.
William Moore Nichols (Leeds)	Dec. 5th, 1912.	1940.
Walter James Rees (Sheffield)	Aug. 7th, 1941.	Apr. 4th, 1950.
Gilbert Wooding Robinson (Bangor)	Dec. 2nd, 1920.	May 6th, 1950.
Harold George Tribley (Cheltenham) ...	May 1st, 1919.	May 2nd, 1950.

Correction:

Proc., 1950, p. 77, *delete* James Joseph Cowperthwaite (Salford), elected Apr. 4th, 1946, died Dec. 15th, 1949.

CONGRATULATIONS.

The congratulations of the Society have been conveyed to the following Fellows whose names appear in the Birthday Honours List:

Knight Bachelor.

Wilfred Russell Grimwade (Melbourne).
James Irvine Orme Masson (Sheffield).
James Eckersley Myers (Manchester).

C.B.E.

Harold King (N.W.7).
Arthur James Turner (Lisburn).

ELECTION OF NEW FELLOWS.

The following 36 candidates were elected Fellows of the Society on June 1st, 1950:

Edward Felix Lucien John Anet.
Eric Billingsley Bates.
Arthur David Baynes-Cope.
Robert A. Benkeser.
Denise Elizabeth Bowles.
James Henry Brewster.
Herbert Charles Brown.
Glen Dale Cooper.
Malcolm Charles Crew.
Jack Derrick.
Kenneth Patrick Fellowes.
Geoffrey Ivor Goodfellow.
Ronald Powell Graham.
Lester Dewie Goodchild Hamilton.
George Simms Hammond.
William Frederick Harper.
Albert William Dennis Hartley.
Robin John Richard Hayward.
John Richard Hickman.
Pierre E. Kiener.
Nathan Kornblum.
Alfred Keith Light.
Lawrence Alexander Lord.
Ewan Cameron Martin.
Lothar Martin.
Joseph Miller.
Jacques Raymond Olivier.
Alan John Owen.
James Ivor Phillips.
Kenneth James Rice.
Thomas Atkinson Shaw.
Henry Joseph Shine.
Richard Steedman Staunton.
William Harmer Stevens.
Thomas Strawford.
Thomas Stanley Worthy.

RESEARCH FUND.

The following grants have been awarded from the Research Fund:

Aberystwyth, Edward Davies Chemical Laboratories.

	£	s.	d.
Dr. M. M. Davies. "Physico-chemical studies of carboxylic acid solutions"	20	0	0

Cambridge, University Chemical Laboratory.

Dr. F. N. Lahey. "Australian plant products"	50	0	0

Dublin, Trinity College.

Dr. D. C. Pepper. "Mechanism of ionic polymerisations"	50	0	0

Glasgow, The University.

Dr. J. C. D. Brand. "Steric effects in aromatic substitution"	30	0	0

London, Imperial College.

Dr. B. C. L. Weedon. "Polyene syntheses"	15	0	0

London, Royal Free Hospital School of Medicine.

Dr. F. Kurzer. "Cyanamides. The interaction of arylthioureas and sulphonyl chlorides"	15	0	0

Oxford, Inorganic Chemistry Laboratory.

Dr. J. W. Linnett. "The effect on the fundamental flame speeds of some gaseous mixtures of replacing light hydrogen by heavy hydrogen, both combined and free"	12	5	0

MEETING OF COUNCIL.

A Meeting of Council was held on June 1st, 1950.

The Report of the meeting of the Publication Committee held on May 4th was received, and it was agreed that the length of articles appearing in the Annual Reports might be increased by 50% where it was considered advisable. Consideration of a recommendation that the Society should revert to the pre-war style of type and headings in the *Journal* was deferred.

The Report of the meeting of the Joint Library Committee held on May 24th was received, and the list of books recommended for purchase was approved.

The thanks of the Council have been conveyed to Dr. R. T. Lattey and Mr. W. B. Saville for gifts of the Society's publications.

The resignation of Dr. G. Baddeley as Local Representative for Manchester was accepted with regret, and Dr. G. R. Barker was appointed to this office.

It was reported that Mr. W. J. Weir would represent the Society at the 5th International Congress of Microbiology at Rio de Janeiro in August 1950.

JOURNAL OF THE CHEMICAL SOCIETY, MICROFILM EDITION.

The Chemical Society has entered into an agreement with University Microfilms, Ann Arbor, Michigan, to make issues from January 1950 of *The Journal of the Chemical Society* available to libraries in microfilm form.

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50th ANNIVERSARY OF THE DISCOVERY OF GRIGNARD REAGENTS.

The Society was represented by Professor D. H. Hey and Professor H. Burton at the Celebrations in Lyons on May 13th of the 50th Anniversary of the Discovery of Grignard Reagents. The following Address was presented:

"The President, Council and Fellows of The Chemical Society learn with the greatest pleasure that the University of Lyons will celebrate on the Thirteenth day of May, One Thousand Nine Hundred and Fifty, the Fiftieth Anniversary of the Discovery of the series of organo-magnesium compounds now known universally by the name of their discoverer, Victor Grignard, as 'Grignard Reagents.'

"We recall with pleasure and satisfaction that Victor Grignard, whose important discovery has provided the Chemist with a versatile reagent of very great value in the synthesis of many types of organic compounds, was elected an Honorary Fellow of The Chemical Society in 1920.

"We desire to associate ourselves with our French colleagues and with Scientists throughout the World in paying homage to the memory of this great Chemist, and we send cordial greetings and best wishes for a most successful Meeting.

"Signed on behalf of The Chemical Society:

Eric K. Rideal, *President.*
W. A. Akers, *Treasurer.*
D. H. Hey, H. Burton, *Honorary Secretaries.*"

MEETINGS OUTSIDE LONDON

BIRMINGHAM.

"Crystal Growth," by Professor E. K. Rideal, M.B.E., M.A., D.Sc., F.R.S.

A joint meeting with the University Chemical Society was held in the Chemical Lecture Theatre of the University on March 17th, 1950, with Professor H. W. Melville in the Chair.

Professor Rideal pointed out how crystal faces have different surface energies. Their growth rates are dependent on several factors; the mechanism of commencing a fresh layer, the mechanism and rate of surface mobility, and the specific rates of solution and condensation. Methods can be devised for examining all these factors. Problems of nucleation were also discussed in the light of Von Weimarn's hypothesis concerning the dispersion coefficient, and that of Haber on the effect of time and dispersive forces on the rate of molecular organisation.

A vote of thanks to the Lecturer, proposed by Dr. G. Gilbert, was carried with enthusiasm.

" What is a Chemical Bond? " by Professor C. A. Coulson, F.R.S.

A joint meeting with the University Chemical Society was held in the Chemical Lecture Theatre of the University on May 12th, 1950, with Professor H. W. Melville in the Chair.

Professor Coulson stated that our present description of a chemical bond is resolved into a description of the " electron-patterns " provided by wave mechanics. In general each pattern is localised in the region of the bond, and thus confers upon the bond characteristic properties such as length and energy, which are largely independent of the rest of the molecule. These electron patterns for a bond may be closely represented as the combination of two atomic patterns, which we may thus describe as paired together. Stereochemical considerations, represented by the criterion of maximum overlapping of these atomic orbits, show that they are frequently hybrids of more familiar s, p, d . . . orbits. Such bonds are usually straight (*i.e.*, have axial symmetry); but when, as in *cyclo*propane, there is strain, the bonds may be described as bent. Any failure of the additivity relationships may be interpreted as a partial delocalisation of the pattern for a bond, in which the electrons of the bond are occasionally to be found on other nearby atoms.

The lecture was followed by a discussion, at the conclusion of which a vote of thanks to the Lecturer, proposed by Dr. L. L. Bircumshaw, was carried with acclamation.

APPLICATIONS FOR FELLOWSHIP

(*Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the* Journal *for July* 1950. *Such objections will be treated as confidential. The forms of application are available in the Library.*)

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PAPERS RECEIVED

(List of papers received between May 17th and June 12th, 1950.)

"The ultra-violet spectra of certain substituted aromatic nitro-compounds." By P. Fielding and R. J. W. Le Fèvre.

"The action of Grignard reagents on ethylene oxide anhydro-sugars. Part I. The behaviour of derivatives of 2 : 3-anhydro-α-methylalloside towards methylmagnesium iodide." By F. H. Newth, G. N. Richards, and L. F. Wiggins.

"Amino-acid separations using a strong-base resin." By C. W. Davies, R. B. Hughes, and S. M. Partridge.

"Reactions of organic peroxides. Part III. Oxidation of methyl*cyclo*pentane and methyl*cyclo*hexane." By E. J. Gasson, E. G. E. Hawkins, A. F. Millidge, and D. C. Quin.

"Reactions of organic peroxides. Part IV. Reactions of methyl*cyclo*pentyl and methyl*cyclo*hexyl hydroperoxides." By E. G. E. Hawkins.

"Reactions of organic peroxides. Part V. Reaction of ferrous sulphate with methyl-*cyclo*pentyl and methyl*cyclo*hexyl hydroperoxides." By E. G. E. Hawkins and D. P. Young.

"The synthesis of long-chain aliphatic acids from acetylenic compounds. Part III. The synthesis of linoleic acid." By R. A. Raphael and Franz Sondheimer.

"Heteropolytungstic acids and heteropolytungstates. Part I. 11-Tungstoferric(III) acid and its salts." By John A. Mair.

"Heteropolytungstic acids and heteropolytungstates. Part II. 11-Tungstoaluminic acid, 11-tungstochromic(III), acid 11-tungstomanganic(III), acid and their salts." By JOHN A. MAIR and JOHN L. T. WAUGH.

"Interaction of alcohols with the chlorides of boron and silicon." By W. GERRARD, M. F. LAPPERT, and A. H. WOODHEAD.

"Experiments on the interaction of hydroxy-compounds and phosphorus and thionyl halides in the absence and in the presence of tertiary bases. Part IX." By W. GERRARD and R. A. JEFFREYS.

"Germanous oxide and sulphide." By DAVID A. EVEREST and HENRY TERREY.

"The systems zinc oxide–phosphoric oxide–water and manganous oxide–phosphoric oxide–water at temperatures between 25° and 100°." By J. E. SALMON and H. TERRY.

"2 : 5-Dichlorothiophenol and 2 : 5 : 2′ : 5′-tetrachlorodiphenyl disulphide." By W. SOLOMON.

"The action of ionizing radiations and of radiomimetic chemicals on deoxyribonucleic acid. Part I. The action of some compounds of the 'mustard' type." By J. A. V. BUTLER and K. A. SMITH.

"Copper-catalysed decomposition of aliphatic diazo-compounds. Formation of high molecular weight paraffins." By G. D. BUCKLEY, L. H. CROSS, and N. H. RAY.

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"The reactivity of 2-naphthols and 2-naphthylamines." By F. BELL and W. H. HUNTER.

"Insecticidal activity and chemical constitution. Part II. Synthesis of some DDT isosteres." By E. JOHN SKERRETT and D. WOODCOCK.

"Experiments on the interaction of hydroxy-compounds and phosphorus and thionyl halides in the absence and in the presence of tertiary bases. Part X." By W. GERRARD and E. G. G. WHITBREAD.

"The addition of osmium tetroxide to dinaphthylethylenes." By C. A. COULSON.

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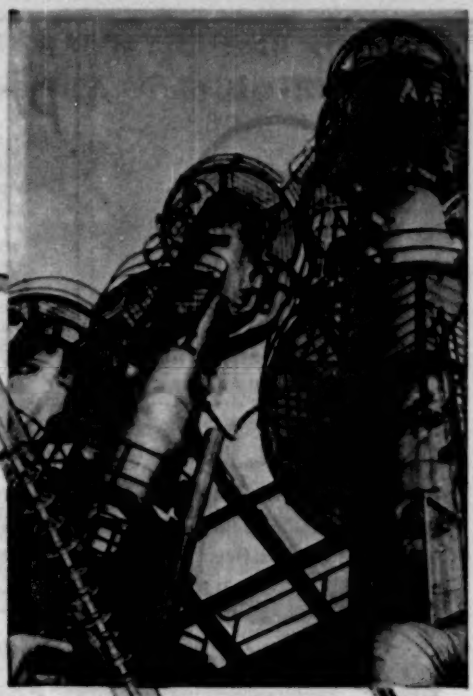

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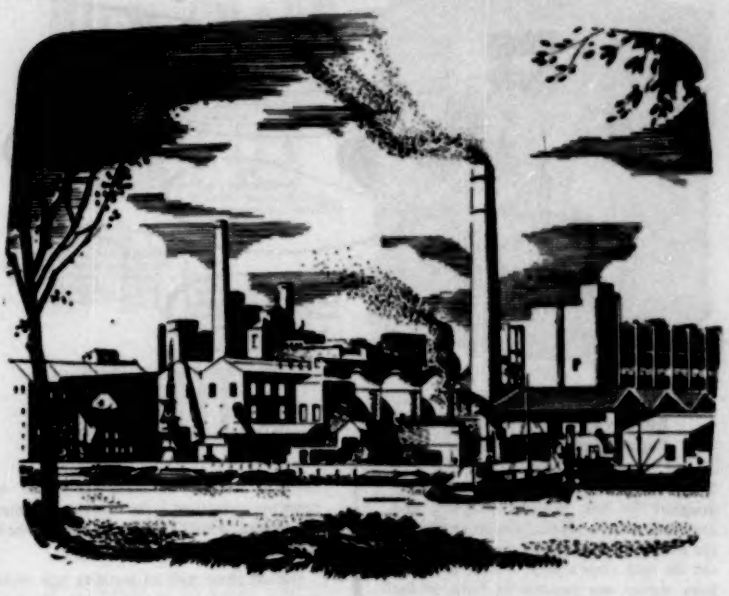

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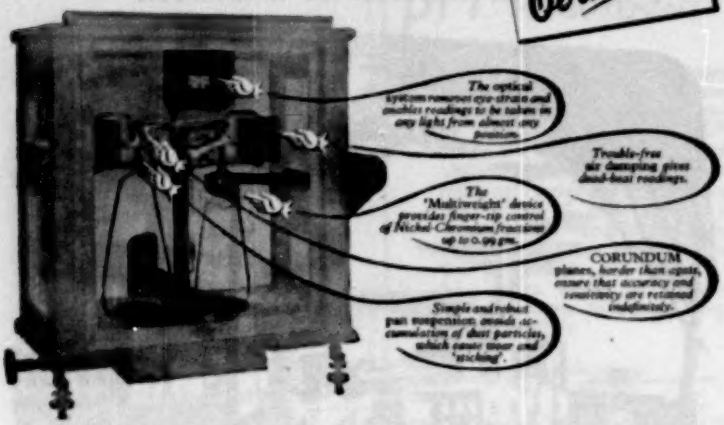
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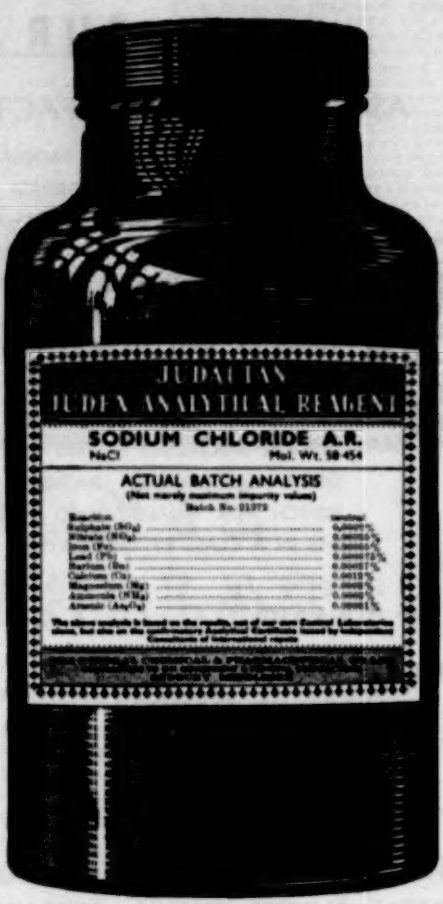

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Pearce, R. S. See Badger, G. M., 1700.
Pindar, A. R. See Haworth, R. D., 1776.
Pollock, J. R. A. See Cook, A. H., 1892, 1898, 1947.
Pritchard, H. O., and Skinner, H. A., 1928.
Reece, C. H. See Rowden, K., 1686, 1969.
Rigby, W., 1907.
Robertson, A., and Whalley, W. B., 1882.
Robertson, A. See also Collins, D. A., 1876.
Rule, H. G., Campbell, N., McGregor, A. G., and Woodman, A. A., 1816.
Schubert, C. I. See Pausacker, K. H., 1814.
Shen, T. Y., and Whiting, M. C., 1772.
Skinner, H. A. See Pritchard, H. O., 1928.
Springall, H. D. See Foss, M. E., 1691.
Stephens, F. F., and Bower, J. D., 1722.
Strickland, J. D. H. See Cosgrove, J. D., 1845.
Stuart, E. R. See Cocker, W., 1781.
Swan, J. M. See Cook, A. H., 1947.
Thomas, A. T. See Foss, M. E., 1691.
Thomas, G. H. See Cook, A. H., 1884, 1888.
Thomson, R. H., 1737.
Thomson, R. H. See also Lyons, J. M., 1971.
Thompson, W. H. See Cocker, W., 1781.
Turner, E. E. See Beeby, M. H., 1923, Glaser, J., 1753, and Hall, D. M., 1842.
Urbański, T. See Foss, M. E., 1691.
Wadman, W. H. See Hough, L., 1702.
Wardill, J. E. See Hudson, R. F., 1729.
Waters, W. A. See Bickel, A. F., 1764.
Whalley, W. B. See Robertson, A., 1882.
Wheeler, T. S. See Gowan, J. E., 1925.
Whiting, M. C. See Shen, T. Y., 1772.
Whyte, D. R. A. See Cocker, W., 1781.
Wiggins, L. F. See Newth, F. H., 1734.
Williams, J. M. See Hey, D. H., 1678.
Williams, R. T. See Parke, D. V., 1757, 1760.
Woodman, A. A. See Rule, H. G., 1816.
Young, G. T. See Le Quesne, W. J., 1954, 1959.

ERRATA.

Vol.	Page.	Line.	
1948	1672	6 •	*for* R. H. Holland *read* R. A. Holland.
1949	1038	13	*for* 2-o-carboxybenzoylindonoglyoxaline *read* 2-o-carboxybenzoylindenonoglyoxaline.
	1065		*Formula* (VII.) *should read*
	1916	2 •	*for* Chada *read* Chadha.
	2895	17	*for* Halleman *read* Hellerman.
	2999	9	*for* 0·1 ml. *read* 0·1 mol.
	3038	6 •	*for* (I; R = Me, R = H) *read* (I; R = Me, R′ = H).
	3039	25	*for* (VII; R = CHO, R′ = Me) *read* (VII; R = Me, R′ = CHO).
	3277	34, 35	for 1 : 2 : 3-*Trimethoxy-5-methylnaphthalene* read 1 : 2 : 3-*Trimethoxy-8-methylnaphthalene*.
	3349	20	*for* heptanone *read* heptenone.
	S233	21	*before* and acetic anhydride (10 c.c.) *add* sodium iodide (1 g.),.
	S244	2 •	*for* 2969 *read* 2896.
	S299	22	*for* molarity *read* molality.
		17 •	*for* molarities *read* molalities.
	S300	5 •	(twice) *for* Molarities *read* Molalities.
	S301	12	(twice) *for* Molarities *read* Molalities.
		16 •	*for* Molarity *read* Molality.
	S318	27, 22	*for* 5·325 *read* 5·34.
	S321		
	S373		last line of footnote *for* duration *read* durations.
1950	173	2 •	*for* Mrs. *read* Mr.
	382	13	*for* $\varepsilon = 1{\cdot}31 \times 10^{2n}\nu$ *read* $\varepsilon = 1{\cdot}31 \times 10^{2n}\nu$,
		20	*for* $\varepsilon_{max.}^{(1)} = 1{\cdot}31 \times 10^{2n}\nu$, $\varepsilon_{max.}^{(2)} = 1{\cdot}74 \times 10^{2n}n$ for polyenes and polycyclic hydrocarbons, $\varepsilon_{max.}^{(3)} = 1{\cdot}74 \times 10^{2n}(n+1)$ for diphenylpolyenes. *read* $\varepsilon_{max.}^{(1)} = 1{\cdot}31 \times 10^{2n}\nu$, $\varepsilon_{max.}^{(2)} = 1{\cdot}74 \times 10^{4}n$ for polyenes and polycyclic hydrocarbons, $\varepsilon_{max.}^{(3)} = 1{\cdot}74 \times 10^{4}(n+1)$ for diphenyl-polyenes.
	550	4 •	*for* CCl_4 — — — — — — — — *read* CCl_4 1 1 1 1 1 1 1 1
	698	8	*for* $C_{20}H_{30}O$ *read* $C_{20}H_{44}O$.
	746	4	for cyclo*Hexano*cyclo*heptane-2′-acetic acid* read cyclo*Hexano*cyclo*heptane-2′-acetic acid*.
	779		Equation at the bottom of the page *for* SH^- *read* SH^+.
	824		Legend to Fig. 1 *for* B, the same $+7{\cdot}8 \times 10^{-4}$N-KOH; C, the same +0·025N-KOH *read* C, the same $+1{\cdot}6 \times 10^{-4}$N-KOH; B, the same +0·025N-KOH.
	826		Legend to Fig. 4 *for* B *read* C; *for* C *read* B.
	885	4 •	*for* usual *read* unusual.
	1030	17	*for* 1 m-mol. *read* 0·81 m-mol.
		23	*for* 67% *read* 82%.
		24	*for* 73% *read* 89%.
		28	*for* $\varepsilon_{max.} = 8000$ *read* $\varepsilon_{max.} = 9800$.
	1275	28	*for* followed by (4) and (5), *read* followed by (5) and (6).
	1394	19	*after* experiments *add* (carried out at 200°, 250°, 300°, and 330°, respectively).
	1482	8	*for* 1 : 6-compound *read* 1 : 5-compound.
	1484	22 •	*for* m. p. 295° *read* m. p. 274°.
	1484	21 •	*for* m. p. 274° *read* m. p. 295°.

• From bottom.

INFORMATION FOR CANDIDATES FOR FELLOWSHIP

The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows who pay the annual subscription of £3 10s. have the following privileges.

1. To receive a selection of the Society's publications. Publications in excess of those allowed under the Annual Subscription may be purchased at favourable rates. Details are available on application to the General Secretary.
2. To consult and borrow the books in the Library.
3. To attend meetings of the Society both in London and outside London, and to introduce two guests thereto.
4. To apply for research grants.
5. To submit original papers for publication in the *Journal*.

Fellows under the age of 25, who so wish, may pay an annual subscription of £1 15s. and enjoy all the privileges accorded to those paying the full subscription except that the choice of publications is limited.

PUBLICATIONS

(*a*) *The Journal of the Chemical Society*, which is published monthly, contains the results of investigations which cover the whole field of pure chemistry.

(*b*) *British Abstracts*.—The Society collaborates with the Society of Chemical Industry, the Physiological Society, the Biochemical Society, and other organisations in contributing to the maintenance of the Bureau of Abstracts, which issues every month abstracts of papers dealing with all branches of pure and applied chemistry, physiology, and anatomy published in all parts of the world.

British Abstracts A is divided into three sections: AI, General, Physical, and Inorganic Chemistry; AII, Organic Chemistry; AIII, Physiology and Biochemistry, including Anatomy.

(*c*) *Annual Reports on the Progress of Chemistry*.—These reports, written by experts, summarise the important new advances in pure chemistry and related subjects.

(*d*) *Quarterly Reviews* are composed of articles on selected topics from the whole field of chemistry.

LIBRARY

The extensive reference and lending library of the Chemical Society contains over 47,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London*.—Scientific Meetings of the Society are held usually on the first and third Thursdays of each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London*.—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

Forms of Application for Fellowship can be obtained from THE GENERAL SECRETARY, THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.

NOTICES TO AUTHORS OF PAPERS

SUBMISSION OF PAPERS. 1. All Scientific Communications for the *Journal* should be addressed to "The Honorary Secretaries, The Chemical Society, Burlington House, W.1." Papers to be read before a meeting of the Society are selected by the Honorary Secretaries.

2. A paper is not normally considered for publication in the *Journal* unless at least one of the authors is a Fellow of the Society, but in exceptional circumstances the Council is prepared to consider papers submitted by non-Fellows.

3. Communications which have appeared or have been accepted for publication with essentially the same scientific content in another Journal or freely available printed work shall not be published in the *Journal* of the Society unless this course is approved by the Council.

4. Papers are accepted by the Society on the understanding that the authors have obtained any necessary authority to publish.

5. The Society reserves the right to retain all papers sent to it, and authors are therefore advised to keep copies. When papers have been accepted for publication the authors are not at liberty, save by permission of the Council, to withdraw or delay them, or to publish them elsewhere until they have appeared in the *Journal* of the Society. Papers which are retained by the Council after being judged unsuitable for publication in the *Journal* are deposited in the Archives of the Society; this right is not usually exercised in regard to illustrations.

MANUSCRIPT. 6. All manuscripts must be top copies, clearly typed, on non-absorbent paper, in double-line spacing and on one side only. Footnotes add considerably to the cost of printing, and should not be used unless necessary.

7. The address to which proofs are to be sent must be given on the front page of every paper.

RESPONSIBILITY. 8. Authors are solely responsible for the factual accuracy of their papers. They are particularly requested to verify references and to indicate positions of cross-references.

SUMMARY. 9. Every paper must be prefaced by a short summary (50—250 words) setting forth briefly and in simple language the objects of the investigation and the results obtained. The summary should give any chemist a clear idea of what the investigation has achieved and should be independent of the main text. "Notes" do not require a summary.

STYLE. 10. Authors are requested to see that their papers conform, as nearly as possible, to the normal style, conventions, and conciseness of the *Journal*.

NOMENCLATURE. 11. Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed in the *Journal* are reviewed in "Modern Chemical Nomenclature," by Dr. Clarence Smith (*J.*, 1936, 1067); reprints of this paper may be obtained by Fellows, price 2*d*. post free, from the General Secretary. Much valuable discussion will be found in "British Chemical Nomenclature," by Dr. A. D. Mitchell [Edward Arnold & Co., 1948]. Authors should choose their symbols from the "Report of a Joint Committee of the Chemical Society, Faraday Society, and the Physical Society on Symbols for Thermodynamical and Physico-Chemical Quantities and Conventions Relating to their Use," copies of which may be obtained by Fellows, price 4*d*. post free, from the General Secretary.

NEW COMPOUNDS. 12. New compounds should be indicated by underlining the name at its first mention (excluding headings) in the Experimental section *only*, and by giving analytical results in the form: "Found: ———, ——— requires ———." Analytical results for compounds which have previously been adequately described in the literature should be given in the form: "Found: ———. Calc. for ———: ———."

ILLUSTRATIONS. 13. Illustrations accompanying the papers must be carefully drawn, preferably *twice* the size of the finished block (max. width 5 inches), *in Indian ink, on good white cartridge paper* (graph paper with faint blue lines is acceptable). Any illustration which seriously exceeds four times the size of the finished block will be returned to the author for re-drawing to a smaller scale. Lettering on the drawings, whether on the margin or in the body of the drawing, must not be in ink but must be inserted *clearly but lightly in pencil*. *Margins* of at least two inches must be left. Authors may, if they wish, submit in the first place clearly drawn pencil sketches instead of the completed diagrams, which, however, must be supplied before publication. Further information can be obtained from the Editor.

PROOFS. 14. Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors. See also paragraph 7.

PREPRINTS. 15. Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs.

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

1948	*Liabilities.*		1949		1948	*Assets.*		1949	
£ s. d.		£ s. d.	£ s. d.	£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.
— — —	To Sundry Creditors			2 6 10	1101 7 11	By Investments as per Schedule (cost or value when acquired)		1101 7 11	
1043 3 1	„ Excess of Assets over Liabilities as per last Balance Sheet		1146 19 9		43 11 10	„ Cash at Bank		89 8 8	
— — —	*Add* Excess of Income over Expenditure for year		44 10 0						
1043 3 1			1191 9 9						
101 3 4	*Deduct* Excess of Expenditure over Income for year			1191 9 9					
		1146 19 9		£1193 16 7	£1146 19 9			£1193 16 7	
£1146 19 9									

SPECIAL LECTURES FUND.

£ s. d.		£ s. d.	£ s. d.	£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.
— — —	To Sundry Creditors			1 14 4	1565 5 0	By Investment as per Schedule (cost or value when acquired)		1514 5 0	
1238 4 6	„ Excess of Assets over Liabilities as per last Balance Sheet		1562 0 11		316 16 11	„ Cash at Bank		101 3 0	
— — —	*Add* Excess of Income over Expenditure for year		23 19 9						
166 8 0	*Add* Net Profit on change of Investment ...								
1404 12 6			1585 19 8						
31 8 7	*Deduct* Excess of Expenditure over Income for year			1585 19 8					
		1562 0 11		£1616 8 0	£1562 0 11			£1616 8 0	
£1562 0 11									

THE FARADAY LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.	£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.
— — —	To Sundry Creditors			13 9	369 4 0	By Investment as per Schedule (cost or value when acquired)		439 4 0	
437 0 0	„ Excess of Assets over Liabilities as per last Balance Sheet		470 13 9		101 9 9	„ Cash at Bank		45 6 9	
33 7 7	*Add* Excess of Income over Expenditure for year		13 3 1						
		470 13 9		483 17 0					
				£484 10 9	£470 13 9			£484 10 9	
£470 13 9									

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1949.

THE TILDEN LECTURE FUND.

1948 £ s. d.	£ s. d.	*Liabilities.*	1949 £ s. d.	£ s. d.
	35 4 0	To Sundry Creditors		39 8 10
1966 2 2		„ Excess of Assets over Liabilities as per last Balance Sheet	2014 2 2	
48 0 0		*Add* Excess of Income over Expenditure for year		
2014 2 2			2014 2 2	
		Deduct Excess of Expenditure over Income for year	24 11 2	
	2014 2 2			1989 11 1
	£2049 6 2			£2029 19 11

1948 £ s. d.	£ s. d.	*Assets.*	1949 £ s. d.
1879 14 10		By Investments as per Schedule (cost or value when acquired)	1879 14 10
160 11 8		„ Cash at Bank (including Deposit)	137 6 1
£2039 6 2			£2029 19 11

CENTENARY FUND.

£ s. d.	£ s. d.		d.	£ s. d.
		To Sundry Creditors		77 15 10
		„ Capital Account:		
11,797 7 1		Contributions under Deeds and Donations brought forward	14,624 9 4	
3,199 18 11		*Add* Contributions under Deeds and Donations for year	2,707 17 6	
14,996 6 0			17,332 6 0	
801 16 6		*Deduct* Net Loss on change of Investments		
	14,624 9 4			17,332 6 6
		„ Excess of Income over Expenditure for year	87 9 2	
61 17 11		*Deduct* Excess of Expenditure over Income brought forward		
99 16 10		*Add* Excess of Income over Expenditure brought forward	32 2 1	
	33 2 1			120 11 3
	£14,657 11 5			£17,530 13 9

£ s. d.	£ s. d.		£ s. d.
1,197 9 9		By Sundry Debtors	
13,006 3 4		„ Investments as per Schedule (cost or value when acquired)	17,198 3 4
701 18 4		„ Cash at Bank	332 10 5
£14,657 11 5			£17,530 13 9

THE ROBERT JOHN FLINTOFF TRUST.

£ s. d.	£ s. d.		£ s. d.
		To Cash received from Executors	1000 0 0
		Add Excess of Income over Expenditure for year	3 17 9
			£1003 17 9

£ s. d.	£ s. d.		£ s. d.
		By Investments as per Schedule (cost or value when acquired)	1000 0 0
		„ Cash at Bank	3 17 9
			£1003 17 9

GENERAL PURPOSES.

Nominal Details.	Cost or Value when Acquired.	Market Value 31st December, 1949.
	£ s. d.	£ s. d.
£2438 18s. 9d. 3½% Conversion Loan, 1961, or after	1994 10 6	2261 2 11
£3406 2s. 6d. 3% Funding Loan, 1959/69	3429 11 5	3335 17 7
£2400 14s. 3d. 3% Savings Bonds, 1960/70	2418 11 0	2325 14 3
£3000 3% Savings Bonds, 1965/75	3006 4 5	1896 0 0
£4747 4s. 8d. 3% British Transport Guaranteed Stock, 1978/88	3704 9 8	4279 10 1
£2646 1s. 6d. 3% British Electricity Guaranteed Stock, 1968/73	2349 4 5	2423 10 7
£1900 3½% Defence Bonds	1900 0 0	1900 0 0
£2400 3½% Bristol Corporation Debenture Stock, 1967	2370 2 0	2304 0 0
£1552 3½% London County Consolidated Stock, 1954/59	1539 7 6	1396 10 0
£2000 3% London County Consolidated Stock, 1961/67	2032 10 0	2010 0 0
£2500 3% Commonwealth of Australia Registered Stock, 1964/66	2309 7 6	2432 10 0
£A3170 4% Commonwealth of Australia Treasury Bonds, 1961	1833 15 0	1765 8 3
£A430 4% Commonwealth of Australia Treasury Bonds, 1961	719 3 7	678 6 0
	£25,896 13 9	£27,800 9 7

PUBLICATIONS FUND.

£2240 19s. 8d. 3½% Conversion Loan, 1961, or after	1566 16 4	2125 6 5
£1000 3% Savings Bonds, 1955/65	1000 0 0	991 5 0
£2261 1s. 11d. 3% Savings Bonds, 1960/70	2276 1 11	2190 9 0
£2175 13s. 4d. 3% British Transport Guaranteed Stock, 1978/88	1979 1 4	1956 2 0
£2000 3% British Electricity Guaranteed Stock, 1968/73	2002 10 0	1863 15 0
£1500 3% Commonwealth of Australia Registered Stock, 1964/66	1204 10 0	1166 0 0
£981 15s. 0d. 3% Southern Rhodesia Stock, 1971/73	1000 0 0	933 9 8
	£10,979 19 7	£11,220 6 7

SPECIAL RESERVE FUND.

£1300 3½% Defence Bonds	1300 0 0	1300 0 0
£1500 3% Savings Bonds, 1955/65	1500 0 0	1498 17 6
£2649 10s. 6d. 3% Liverpool Corporation Stock, 1954/64	2647 2 0	2634 11 10
£3000 3½% Funding Loan, 1954/61	3011 5 0	2970 0 0
	£8458 7 0	£8361 9 4

RESEARCH FUND.

£4177 16s. 1d. 3½% Conversion Loan, 1961, or after	3635 16 5	3927 2 0
£500 Defence Bonds, 6th issue	500 0 0	500 0 0
£4000 3% Savings Bonds, 1960/70	4000 0 0	3875 0 0
£3755 2s. 1d. 3% British Transport Guaranteed Stock, 1978/88	3847 19 5	3379 11 11
£3719 2s. 9d. 3% British Electricity Guaranteed Stock, 1968/73	3734 1 2	3540 7 10
£4000 3% Commonwealth of Australia Registered Stock, 1964/66	4015 0 0	3860 0 0
	£19,491 17 8	£19,081 3 6

ROBERT JOHN FLINTOFF TRUST.

£522 2s. 2d. 3½% Conversion Loan, 1961, or after	500 0 0	421 14 5
£548 18s. 4d. 3% British Transport Guaranteed Stock, 1978/88	500 0 0	481 7 5
	£1000 0 0	£903 1 10

SPECIAL PUBLICATIONS FUND.

Nominal Details.	Cost or Value when Acquired.	Market Value 31st December, 1949.
	£ s. d.	£ s. d.
£718 4s. 10d. 3½% Conversion Loan, 1961, or after	641 3 4	672 10 8
£746 1s. 0d. 3% British Transport Guaranteed Stock, 1978/88	719 18 9	671 8 11
£780 3% British Electricity Guaranteed Stock, 1968/73	750 18 9	713 18 1
	£2011 10 10	£2057 17 8

STAFF PENSIONS FUND.

£114 1s. 11d. 3½% Conversion Loan, 1961, or after	98 2 3	107 5 0
£150 3½% National War Bonds, 1951/53	150 0 0	161 10 7
£170 3% Savings Bonds, 1955/65	170 0 0	170 0 0
£315 2s. 7d. 3½% Funding Loan, 1954/61	315 2 9	338 10 6
£2500 3½% Defence Bonds	2500 0 0	2500 0 0
	£3733 4 0	£3784 15 1

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£61 15s. 8d. 3½% Conversion Loan, 1961, or after	60 1 5	60 1 6
£1489 10s. 6d. 3% British Transport Guaranteed Stock, 1978/88	1041 6 6	1040 11 6
	£1101 7 11	£1100 13 0

SPECIAL LECTURES FUND.

£1501 19s. 5d. 3% British Transport Guaranteed Stock, 1978/88	£1515 9 0	£1406 3 0

THE FARADAY LECTURE FUND.

£441 1s. 11d. 3½% Conversion Loan, 1961, or after	£439 4 0	£414 13 7

THE TILDEN LECTURE FUND.

£419 4s. 10d. 3% Funding Loan, 1959/69	366 13 10	456 13 3
194 National Provincial Bank Shares (5 each, £1 paid "B")	678 16 0	667 8 6
£681 19s. 1d. 3% British Transport Guaranteed Stock, 1978/88	620 2 0	613 16 2
£200 3% Metropolitan Water Board (East Water Works) Deb. Stock	168 2 0	177 2 0
	£1073 14 10	£1564 15 11

CENTENARY FUND.

£2477 13s. 11d. 3% Savings Bonds, 1955/65	2461 11 10	2454 0 4
£3500 3% Savings Bonds, 1960/70	3534 7 6	3421 17 6
£1970 1s. 0d. 3% New Zealand Stock, 1973/77	2000 0 0	1884 15 3
£3705 18s. 7d. 3½% Savings Bonds, 1964/67	3500 0 0	3450 0 10
£3500 3% British Electricity Guaranteed Stock, 1968/73	3498 8 9	3179 13 6
£3979 15s. 0d. 3% British Transport Guaranteed Stock, 1978/88	2257 7 8	1941 13 9
£A1000 4% Commonwealth of Australia Treasury Bonds, 1961	2930 7 6	2960 5 11
	£17,109 3 4	£16,514 6 11

W. A. AKERS, Treasurer.

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers of the Society, and certify them to be in accordance therewith. We have also verified the Balances at the Bankers and Investments. An interim payment of £1750 on the Corday-Morgan Memorial Fund has been received from the Public Trustee and is not included in the Accounts this year.

FINSBURY CIRCUS HOUSE,
BLOOMFIELD STREET, E.C.2.
MARCH 14TH, 1950.

W. B. KEEN & CO.
Chartered Accountants.

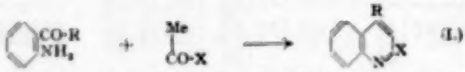
339. *New Therapeutic Agents of the Quinoline Series. Part VII. 2-, 3-, and 4-Pyridylquinolines, 4-Pyridylquinaldines, and 2-Pyridyllepidines.*

By D. H. Hey and J. M. Williams.

Eight of the nine isomeric pyridylquinolines in which the pyridyl group is attached to the heterocyclic ring of the quinoline molecule have been prepared by unambiguous synthetic methods. In addition, the three isomeric 4-pyridylquinaldines as well as the three 2-pyridyllepidines have been prepared.

Previous communications in this series have described the preparation of a number of pyridylquinolines of many different types (Coates, Cook, Heilbron, Hey, Lambert, and Lewis, *J.*, 1943, 401 *et seq.*). With the exceptions of 2-2′-pyridylquinoline, first prepared by Smirnoff (*Helv. Chim. Acta*, 1921, **4**, 802), and two isomerides tentatively regarded as 3-2′- and 3-3′-pyridylquinoline (Coates *et al.*, *loc. cit.*), these communications were largely confined to the preparation of compounds in which the pyridyl group was attached to the carbocyclic ring of the quinoline molecule. Since many of the compounds thus described were found to possess spasmolytic properties in addition to a marked adrenaline action, attention has been redirected to this subject with the object of synthesising further members in which the pyridyl group is attached to the heterocyclic ring of the quinoline, quinaldine, or lepidine molecule. Such studies would also serve to establish the exact identity of the two 3-pyridylquinolines mentioned above. Further, Tscherne (*Monatsh.*, 1901, **22**, 615) has reported the formation of a pyridylmethylquinoline, regarded as 4-4′-pyridylquinaldine, from the cyclisation of the anil of 4-acetoacetylpyridine $PhN{:}CMe{\cdot}CH_2{\cdot}CO{\cdot}X$ (X = 4-pyridyl), but since the isomeric anil $PhN{:}CX{\cdot}CH_2{\cdot}CO{\cdot}Me$ (X = 4-pyridyl) may have been involved, the product may have been 2-4′-pyridyl-lepidine. This reaction has therefore been re-investigated.

The preparation of 2-2′-pyridylquinoline (I; R = H, X = 2-pyridyl) from 2-pyridyl methyl ketone and *o*-aminobenzaldehyde by the method of Smirnoff (*loc. cit.*) has been confirmed, and similar reactions have been carried out with 3-pyridyl and with 4-pyridyl methyl ketone to give the hitherto unknown 2-3′- and 2-4′-pyridylquinoline (I; R = H, X = 3-pyridyl) and (I; R = H, X = 4-pyridyl). All three 2-pyridylquinolines have been further characterised as the picrates.

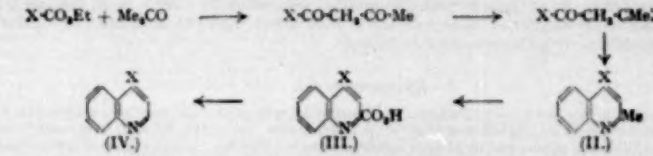


(I.)

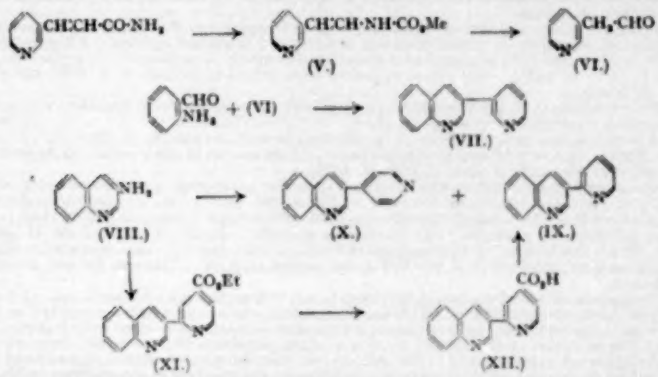
In order to establish the identity of the pyridylmethylquinoline prepared by Tscherne (*loc. cit.*) the three isomeric 2-pyridyl-lepidines (I; R = Me, X = 2, 3, and 4-pyridyl) were prepared by the condensation of the three pyridyl methyl ketones with *o*-aminoacetophenone, and the use of the anils of acetoacetylpyridines in the preparation of pyridylmethylquinolines has been further extended. Kuick and Adkins's procedure (*J. Amer. Chem. Soc.*, 1935, **57**, 143) for the preparation of 3-acetoacetylpyridine from ethyl nicotinate and acetone has been successfully applied to the preparation of the isomeric 2- and 4-acetoacetylpyridine from the ethyl esters of picolinic and *iso*nicotinic acid, respectively. The anils were prepared in acetic acid solution and cyclisation in concentrated sulphuric acid gave 4-2′-, 4-3′-, and 4-4′-pyridylquinaldine (II; X = 2-, 3-, and 4-pyridyl). The compound thus prepared from the anil of 4-acetoacetylpyridine had the same melting point as that reported by Tscherne (*loc. cit.*), and the melting point was depressed on admixture with an authentic specimen of 2-4′-pyridyl-lepidine, prepared as described above. This observation confirms the constitution of Tscherne's compound and shows that the intermediate anils must have the constitution $PhN{:}CMe{\cdot}CH_2{\cdot}CO{\cdot}X$ and not $PhN{:}CX{\cdot}CH_2{\cdot}CO{\cdot}Me$. Mixed melting point determinations with the picrates of the 3′- and 4′-isomerides in the two series could not be carried out, since the compounds in the quinaldine series yielded dipicrates, whereas those of the lepidine series gave monopicrates. The anil of 2-acetoacetylpyridine could not be obtained in crystalline form, unlike those of the 3- and 4-isomerides, and the yield of 4-2′-pyridylquinaldine obtained on cyclisation was low. Further, of the three isomeric 4-pyridylquinaldines, the 2′-isomeride alone gave a monopicrate.

Both 4-3′- and 4-4′-pyridylquinaldine (II; X = 3- and 4-pyridyl) were converted by oxidation with chromic acid of the phthalone into the corresponding quinaldinic acid, isolated as the ethyl ester. The styryl derivatives proved to be less suitable for oxidation. The pure esters were hydrolysed to 4-3′- and 4-4′-pyridylquinaldinic acid (III; X = 3- and 4-pyridyl),

which in turn were subjected to decarboxylation by boiling in quinoline solution containing copper chromite. In this manner 4-3′- and 4-4′-pyridylquinoline (IV; X = 3- and 4-pyridyl) were obtained.



In order to obtain the 3-pyridylquinolines by methods which could leave no doubt concerning the identity of the products, attempts were first made to use an ester of 2-pyridylacetic acid for which convenient preparative methods were available (Clemo, Morgan, and Raper, *J.*, 1935, 1743; Bills and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 957). 3-2′-Pyridylcarbostyril was readily obtained from *o*-aminobenzaldehyde and ethyl 2-pyridylacetate in presence of piperidine, and 2 : 4-dihydroxy-3-2′-pyridylquinoline was obtained in good yield from methyl anthranilate and ethyl 2-pyridylacetate, but attempts to replace the hydroxyl groups in these compounds by chlorine (with phosphorus oxychloride and pentachloride) or by hydrogen (with phosphorus and iodine) were unsuccessful. By means of a Claisen condensation ethyl formyl-2-pyridylacetate was obtained in good yield from ethyl formate and ethyl 2-pyridylacetate, but attempts to cyclise the anil derived from this ester were abortive. Several unsuccessful attempts were also made to prepare 2-pyridylacetaldehyde, which should react with *o*-aminobenzaldehyde to give 3-2′-pyridylquinoline. Thus, the action of 2-picolyl-lithium on ethyl formate or on ethyl orthoformate led to products of doubtful aldehydic properties and the product obtained from the simultaneous hydrolysis and decarboxylation of ethyl formyl-2-pyridylacetate was of uncertain character. On the other hand, 3-pyridylacetaldehyde (VI) was prepared in solution by the hydrolysis of methyl 2-3′-pyridylvinylcarbamate (V), which in turn was obtained by the Hofmann rearrangement of β-3-pyridylacrylamide (cf. Panizzon, *Helv. Chim. Acta*, 1941, **24**, 24E) in methyl alcohol using a concentrated alkaline solution of sodium hypochlorite. Condensation of this aldehyde with *o*-aminobenzaldehyde gave 3-3′-pyridylquinoline (VII), which was characterised as the dipicrate. For purposes of comparison the 3-pyridylquinolines previously described by Coates *et al.* (*loc. cit.*) were prepared from diazotised 3-aminoquinoline (VIII) and pyridine, but neither of these proved to be identical with the authentic specimen of 3-3′-pyridylquinoline from evidence obtained from mixed melting point determinations on the picrates. In order to establish the identity of the isomerides obtained in the reaction between diazotised 3-aminoquinoline and pyridine a reaction was conducted between diazotised 3-aminoquinoline (VIII) and ethyl *iso*nicotinate which, it was expected, would yield mainly ethyl 2-3′-quinolyl*iso*nicotinate (XI) but which, in any case, could not give rise to substitution at the



4-position. Hydrolysis of the product gave an acid (XII), which on decarboxylation gave a 3-pyridylquinoline (IX) identical with one of the products obtained as described above from the reaction between diazotised 3-aminoquinoline and pyridine. This compound must therefore be 3-2′-pyridylquinoline, in agreement with the original suggestion by Coates *et al.* (*loc. cit.*), but their second isomeride would now appear to be 3-4′-pyridylquinoline (X), although this conclusion requires confirmation by an independent synthesis.

Experimental.

2-2′-Pyridylquinoline (4·1 g.) was prepared by Smirnoff's method (*loc. cit.*) by the condensation of 2-pyridyl methyl ketone (5 g.) (Kolloff and Hunter, *J. Amer. Chem. Soc.*, 1941, **63**, 490) with *o*-aminobenzaldehyde (5 g.) in dilute potassium hydroxide solution (20 c.c.; 0·01%). After repeated crystallisation from light petroleum the base melted at 98° and the picrate at 182—183°. Smirnoff quotes m. p. 99° and 182—183° for the free base and picrate, respectively.

2-3′-Pyridylquinoline.—A solution of 3-pyridyl methyl ketone (5 g.) (Kolloff and Hunter, *loc. cit.*) and *o*-aminobenzaldehyde (5 g.) in dilute alcoholic potassium hydroxide (20 c.c.; 0·01%) was heated on a water-bath for one hour. The oil which separated on addition of water was extracted with ether. The viscous liquid, after removal of the ether, partially crystallised on being kept. The solid was separated from oily residues by spreading on a porous plate; repeated crystallisation from light petroleum (b. p. 60—80°) gave 2-3′-*pyridylquinoline* (3 g.) in robust rhombic crystals, m. p. 66·5° (Found: C, 81·2; H, 4·9. $C_{14}H_{10}N_2$ requires C, 81·5; H, 4·9%). The *picrate* crystallised from acetone–alcohol in fine yellow needles which sintered at 185° and melted at 199° (Found: C, 55·3; H, 3·3. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires C, 55·2; H, 3·0%).

2-4′-Pyridylquinoline.—4-Pyridyl methyl ketone (4·2 g.) (Kolloff and Hunter, *loc. cit.*) and *o*-aminobenzaldehyde (4·2 g.) were condensed under identical conditions to those described above to give 2-4′-*pyridylquinoline* (5·3 g.), which crystallised from light petroleum (b. p. 80—100°) in leaflets, m. p. 96° (Found: C, 81·6; H, 4·8%). The *picrate* separated from acetone in fine yellow needles which sintered at 180° and melted at 207° (Found: C, 55·5; H, 3·2%).

2-2′-Pyridyl-lepidine.—To a solution of *o*-aminoacetophenone (3 g.) and 2-pyridyl methyl ketone (3 g.) in alcohol (15 c.c.) was added aqueous sodium hydroxide (0·05 c.c.; 20%), and the mixture was boiled for eighteen hours under reflux on a water-bath. Most of the alcohol was then distilled from the mixture, and the oil which separated on addition of water was extracted with ether. The ethereal extract was dried (K_2CO_3) and, after removal of the ether, the residue was distilled under reduced pressure to give 2-2′-*pyridyl-lepidine* (3·1 g.; b. p. 156°/0·5 mm.), which separated from light petroleum (b. p. 60—80°) in needles, m. p. 67° (Found: C, 81·3; H, 5·2. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·5%). The *picrate* separated from alcohol in fine needles, m. p. 160° (Found: C, 55·8; H, 3·0. $C_{15}H_{12}N_2,C_6H_3O_7N_3$ requires C, 56·1; H, 3·4%).

2-3′-Pyridyl-lepidine.—*o*-Aminoacetophenone (3 g.) and 3-pyridyl methyl ketone (3 g.) were condensed under identical conditions to those described above for 2-2′-pyridyl-lepidine; 2-3′-*pyridyl-lepidine* (3·3 g.; b. p. 176—180°/0·7 mm.) separated from light petroleum (b. p. 60—80°) in needles, m. p. 66·5° (Found: C, 81·7; H, 5·5%). The *picrate* separated from dioxan in needles, m. p. 219—220° (Found: C, 56·2; H, 3·4%).

2-4′-Pyridyl-lepidine.—*o*-Aminoacetophenone (3 g.) and 4-pyridyl methyl ketone (3 g.) were condensed under identical conditions to those given above. 2-4′-*Pyridyl-lepidine* (3·0 g.; b. p. 178°/0·7 mm.) separated from benzene–light petroleum (b. p. 60—80°) in hard needles, m. p. 101—102° (Found: C, 81·7; H, 5·5%). The *picrate* separated from dioxan–*cyclo*hexanone in fine needles, which melted with decomposition at 250—252° (Found: C, 55·8; H, 3·5%).

The three acetoacetylpyridines were prepared from the appropriate pyridinecarboxylic ester and acetone by the modified conditions described by Kuick and Adkins (*loc. cit.*) for the preparation of 3-acetoacetylpyridine. 2-Acetoacetylpyridine (b. p. 97—98°/0·4 mm.), prepared in 55% yield, separated from light petroleum (b. p. 40—60°) in hard needles, m. p. 51°. Micko (*Monatsh.*, 1896, **17**, 442) gives m. p. 49—50° for this ketone. 4-Acetoacetylpyridine (b. p. 143—145°/0·4 mm.), prepared in 52% yield, separated from light petroleum (b. p. 60—80°) in fine needles, m. p. 63°. Tscherne (*loc. cit.*) gives m. p. 62° for this ketone.

4-2′-Pyridylquinaldine.—2-Acetoacetylpyridine (5 g.), aniline (2·8 g.), and acetic acid (2·5 g.) were heated at 80° for four hours. The oil which was liberated on pouring the mixture on crushed ice failed to crystallise on being kept. The oil was therefore extracted with ether, the ether extract dried (K_2CO_3), and, after concentration of the extract to 30 c.c., light petroleum (b. p. 40—60°) was added until a turbidity appeared in the solution. The mixture was then boiled with animal charcoal and filtered. The pale yellow oil resulting after evaporation of the filtrate was dissolved in concentrated sulphuric acid (25 c.c.; *d* 1·84) and heated in an oil-bath at 110° for two hours. When the cold dark-coloured mixture was poured on crushed ice and the acid neutralised with aqueous ammonia an oil separated which was extracted with ether. After removal of the ether there remained a viscous oil, which partly solidified on cooling. The solid, separated from oily residues by spreading on a porous plate, was repeatedly crystallised from light petroleum (b. p. 60—80°) and gave 4-2′-*pyridylquinaldine* (0·5 g.) in needles, m. p. 84° (Found: C, 82·0; H, 5·6. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·5%). The *picrate* separated from dioxan in fine orange needles, m. p. 186—187° (Found: C, 56·4; H, 3·9. $C_{15}H_{12}N_2,C_6H_3O_7N_3$ requires C, 56·1; H, 3·4%).

4-3′-Pyridylquinaldine.—3-Acetoacetylpyridine (5 g.), aniline (2·8 g.), and acetic acid (2·5 g.) were heated at 80° for four hours. The mixture was poured on crushed ice (50 g.) and after the acetic acid had been neutralised with sodium carbonate the solid which separated was filtered from the solution, washed with water, and dried in a vacuum desiccator ($CaCl_2$). Crystallisation from light petroleum (b. p. 60—80°) gave the *anil* (5·7 g.) in yellow platelets, m. p. 83° (Found: C, 75·5; H, 5·8. $C_{19}H_{14}ON_2$

requires C, 75·65; H, 5·9%). The anil (5 g.) was dissolved in cold concentrated sulphuric acid (25 c.c.; *d* 1·84) and heated in an oil-bath at 105° for two hours. The solution now showed a green fluorescence. The mixture was poured on crushed ice, and made alkaline with ammonia solution, and the liberated oil extracted with ether. The extract was dried (K_2CO_3) and after removal of the solvent the residue was distilled under reduced pressure to give **4-3′-*pyridylquinaldine*** (3·5 g.; b. p. 150—152°/0·5 mm.), which separated from light petroleum in cubic crystals, m. p. 107° (Found: C, 82·1; H, 5·2%). The picrate, prepared in the normal manner, decomposed on crystallisation from dioxan–*cyclo*hexanone. It was therefore prepared by mixing hot acetone solutions of the base and picric acid. After cooling, the crystals were filtered off and washed with cold acetone. The *dipicrate* thus prepared sintered at 182° and melted with decomposition at 202—203° (Found: C, 47·5; H, 3·0. $C_{15}H_{12}N_2,2C_6H_3O_7N_3$ requires C, 47·8; H, 2·8%).

4-4′-*Pyridylquinaldine*.—4-Acetoacetylpyridine (5 g.), aniline (2·8 g.), and acetic acid (2·5 g.) were heated together at 80° for four hours. The *anil* (5·5 g.) obtained on treatment of the mixture with ice and water and neutralisation of the acid with sodium carbonate, separated from light petroleum (b. p. 60—80°) in flat needles, m. p. 101° (Found: C, 75·7; H, 5·6%). Tscherne (*loc. cit.*), who prepared the anil from aniline hydrochloride and the diketone, records m. p. 103°. The anil (5 g.) was condensed under identical conditions to those given above for 4-3′-pyridylquinaldine. 4-4′-Pyridylquinaldine (4·0 g.; b. p. 162—164°/0·5 mm.) separated from light petroleum (b. p. 60—80°) in hard needles, m. p. 103° (Found: C, 81·7; H, 5·6%). The melting point on admixture with 2-4′-pyridyl-lepidine was found to be *ca.* 80°. Tscherne (*loc. cit.*) records m. p. 101—102° for the cyclised product. The *dipicrate* separated from dioxan in orange needles, m. p. 186—187° (Found: C, 47·9; H, 2·9%).

4-3′-*Pyridyl-2-styrylquinoline*.—A mixture of 4-3′-pyridylquinaldine (7·2 g.), benzaldehyde (3·13 g.), and acetic anhydride (3·4 g.) was boiled under reflux for thirty hours. The mixture was then distilled with steam to remove excess of benzaldehyde. The viscous dark brown oil solidified on cooling and crystallisation from dioxan gave crude **4-3′-*pyridyl-2-styrylquinoline*** (7·8 g.). A sample, after repeated crystallisation from dioxan, melted at 164° (Found: C, 84·9; H, 5·1. $C_{20}H_{14}N_2$ requires C, 85·6; H, 5·2%).

Ethyl **4-3′-*Pyridylquinaldinate*.**—4-3′-Pyridylquinaldine (9 g.) was heated in a sealed tube at 160—170° for eight hours with phthalic anhydride (9 g.) and fused zinc chloride (2 g.). After cooling, the phthalone was dissolved in sulphuric acid (200 c.c.; 66%) and a solution of chromium trioxide (4·8 g.) in the minimum quantity of water was added in one portion. The mixture was maintained at 90° for ½ hour and then the excess of chromic acid was destroyed by the addition of alcohol (5 c.c.). While the mixture was externally cooled by an ice–salt mixture, sodium hydroxide solution was slowly added until a pH of 3 was reached. The mixture was then filtered and the residue was extracted several times with aqueous sodium hydroxide (10%). The combined alkaline extracts and filtrate were evaporated to dryness on a water-bath. The residue, containing much sodium sulphate, was suspended in absolute alcohol (100 c.c.), concentrated sulphuric acid (25 c.c.) was added, and the mixture was heated on a steam-bath for eight hours. It was then poured on crushed ice, and after the acid had been neutralised with aqueous ammonia the ester was extracted with benzene. The benzene extracts were shaken with dilute hydrochloric acid (50 c.c.; 10%); neutralisation of the acid extract with aqueous ammonia caused the immediate precipitation of the ester which, on crystallisation from benzene, gave *ethyl* **4-3′-*pyridylquinaldinate*** (3 g.) in fine needles, m. p. 160—161° (Found: C, 73·35; H, 5·2. $C_{17}H_{14}O_2N_2$ requires C, 73·35; H, 5·1%).

In a second method the styryl derivative (7·8 g.) was oxidised with chromic anhydride as described above for the phthalone and gave ethyl 4-3′-pyridylquinaldinate (0·9 g.) in needles, m. p. 160—161°, from benzene.

Ethyl **4-4′-*Pyridylquinaldinate*.**—4-4′-Pyridylquinaldine (11 g.) was heated in a sealed tube at 160—170° for eight hours with phthalic anhydride (11 g.) and zinc chloride (2·5 g.). The resulting phthalone was oxidised as described above for the 3′-isomeride. The isolation and preparation of the ester were also effected as previously described. *Ethyl* **4-4′-*pyridylquinaldinate*** (1·5 g.) separated from alcohol in fine needles, m. p. 146° (Found: C, 73·3; H, 5·0%).

4-3′-*Pyridylquinaldinic Acid*.—Ethyl 4-3′-pyridylquinaldinate (3·6 g.) was hydrolysed with alcoholic potassium hydroxide. The potassium salt was filtered off and decomposed by dissolving it in the minimum quantity of water and adding acetic acid. The free *acid* (3·1 g.), purified by precipitation from potassium carbonate solution, separated in plates, m. p. 203° (Found: C, 72·0; H, 4·0. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0%).

4-4′-*Pyridylquinaldinic Acid*.—Ethyl 4-4′-pyridylquinaldinate (1·4 g.) was hydrolysed with alcoholic potassium hydroxide. The acid, isolated as described above, gave **4-4′-*pyridylquinaldinic acid*** (1·2 g.), which separated from water in fine needles, m. p. 225° (decomp.) (Found: C, 72·0; H, 4·1%).

4-3′-*Pyridylquinoline*.—4-3′-Pyridylquinaldinic acid (3·0 g.) was boiled under reflux for one hour with copper chromite (0·1 g.) in quinoline (20 c.c.). Most of the quinoline was distilled from the mixture, the last traces being removed by distillation with steam. The residual oil, which failed to crystallise, was dissolved in ether, the solution was filtered, and after removal of the ether the residue was distilled under reduced pressure to give **4-3′-*pyridylquinoline*** (2·2 g.; b. p. 156—157°/1 mm.), which separated from light petroleum (b. p. 60—80°) containing a trace of benzene in cubic crystals, m. p. 74° (Found: C, 81·7; H, 5·2%). The *dipicrate* separated from dioxan in fine needles, m. p. 210—212° having first sintered at 190° (Found: C, 46·5; H, 2·4. $C_{14}H_{10}N_2,2C_6H_3O_7N_3$ requires C, 47·0; H, 2·4%).

4-4′-*Pyridylquinoline*.—4-4′-Pyridylquinaldinic acid (1·2 g.) was decarboxylated under identical conditions to those described above. 4-4′-Pyridylquinoline (0·5 g.; b. p. 152°/0·1 mm.) separated from light petroleum (b. p. 40—60°) in needles, m. p. 83° (Found: C, 81·75; H, 4·8%). The picrate decomposed on crystallisation from dioxan. Hot acetone solutions of the base and picric acid were therefore mixed and the resulting *dipicrate* was found to sinter at 176° and to melt at 225° (Found: C, 47·0; H, 2·4%).

Ethyl **2-*Pyridylacetate*.**—Copper 2-pyridylacetate (44 g.; Bills and Noller, *loc. cit.*) was converted into

ethyl 2-pyridylacetate (20 g.; b. p. 120—121°/15 mm.) by the method described by these authors for the methyl ester. The same ester was also prepared as described by Clemo, Morgan, and Raper (*loc. cit.*).

3-2′-Pyridylcarbostyril.—Ethyl 2-pyridylacetate (5 g.) was heated at 120° in an oil-bath with *o*-aminobenzaldehyde (3·34 g.) in the presence of piperidine (0·5 c.c.). Crystallisation from dioxan of the resulting solid gave *3-2′-pyridylcarbostyril* (5 g.) in fine needles, m. p. 233° (Found: C, 75·6; H, 4·5; N, 12·6. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

2 : 4-Dihydroxy-3-2′-pyridylquinoline.—Coarsely granulated sodium (0·6 g.) was added to a mixture of ethyl 2-pyridylacetate (3·5 g.) and methyl anthranilate (3·2 g.). When the initial reaction had subsided the mixture was heated on a steam-bath for two hours and finally in an oil-bath at 120°. The mixture was cooled and ethyl alcohol (10 c.c.) added. The mixture was then poured into water and neutralised with acetic acid. The white crystalline solid which separated was filtered off and crystallised from acetic acid. *2 : 4-Dihydroxy-3-2′-pyridylquinoline* (3·75 g.) separated in colourless needles, m. p. 290° (Found: C, 70·3; H, 4·2. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2%).

Ethyl Formyl-2-pyridylacetate.—To granulated sodium (0·8 g.) in anhydrous ether (30 c.c.) was added a mixture of ethyl 2-pyridylacetate (5 g.) and ethyl formate (3 g.) in anhydrous ether (10 c.c.). The mixture was mechanically stirred and externally cooled by an ice–salt mixture. After three hours the sodium had all dissolved and the sodio-derivative of ethyl formyl-2-pyridylacetate began to separate. The mixture was shaken with water, and the aqueous solution extracted with ether to remove unchanged starting materials. The aqueous layer was made just acid by the addition of dilute sulphuric acid and the excess of acid was neutralised with sodium hydrogen carbonate. The resulting crystalline solid was filtered off and recrystallisation from light petroleum (b. p. 60—80°) containing a trace of benzene gave *ethyl formyl-2-pyridylacetate* (3·5 g.) in fine needles, m. p. 98° (Found: C, 61·9; H, 5·7. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7%). The ester was rapidly hydrolysed with simultaneous decarboxylation by dilute mineral acids. The resulting solutions showed aldehydic properties, but no aldehyde could be extracted from the solution.

Methyl 2-3′-Pyridylvinylcarbamate.—A concentrated alkaline solution of sodium hypochlorite was prepared by the passage of chlorine (3·5 g.) into a mixture of sodium hydroxide (10 g.), water (15 c.c.), and ice (20 g.) cooled by an ice–salt mixture. The volume was then adjusted to 50 c.c. with cold water. The freshly prepared sodium hypochlorite solution (6·8 c.c.) was added to a solution of β-3-pyridylacrylamide (1·7 g.; Paniazon, *loc. cit.*) in methyl alcohol (20 c.c.). The mixture was warmed on a water-bath for five minutes, and the methyl alcohol was then distilled off under reduced pressure, which caused the separation of a crystalline solid. After ½ hour at 0° the solid was filtered off; recrystallisation from carbon tetrachloride gave *methyl 2-3′-pyridylvinylcarbamate* (1·2 g.) in needles, m. p. 145° (Found: C, 60·3; H, 5·3; N, 16·1. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·6; N, 15·7%).

3-3′-Pyridylquinoline.—Methyl 2-3′-pyridylvinylcarbamate (0·5 g.) was dissolved in absolute alcohol (5 c.c.) and sulphuric acid (1·8 c.c.; 6*N*.) was added to the hot solution. The mixture was gently boiled on a water-bath for five minutes. A test portion of the solution was added to 2 : 4-dinitrophenylhydrazine in sulphuric acid. The *2 : 4-dinitrophenylhydrazone sulphate* separated from the solution almost immediately and after recrystallisation from dilute sulphuric acid melted at 211° with decomposition (Found: C, 39·6; H, 3·1. $C_{15}H_{11}O_4N_5,H_2SO_4$ requires C, 39·1; H, 3·3%). The remainder of the above mixture was neutralised with a solution of sodium ethoxide in alcohol and *o*-aminobenzaldehyde (0·3 g.) was added. The hydrogen-ion concentration was then adjusted to pH 11 with aqueous sodium hydroxide, and the mixture again heated on a water-bath for two hours. Most of the alcohol was then distilled from the solution and the oil liberated on addition of water was extracted with ether. After removal of the ether by distillation the residue solidified on cooling. *3-3′Pyridylquinoline* (0·1 g.) separated from benzene–light petroleum (b. p. 80—100°) in needles, m. p. 124° (Found: C, 81·7; H, 5·1%). The *dipicrate* separated from dioxan in small orange needles which sintered at 180° and melted at 222—223° (Found: C, 47·5; H, 2·5%).

2-3′-Quinolylisonicotinic Acid.—A solution of 3-aminoquinoline (7·7 g.) in concentrated hydrochloric acid (35 c.c.) and water (15 c.c.) was diazotised at 0—5° with a concentrated aqueous solution of sodium nitrite (4 g.). The suspension of the diazonium salt was added in small portions to well stirred ethyl *iso*nicotinate (75 g.) at 50°. After the addition the mixture was warmed to 90° for ten minutes to complete the reaction. The mixture was then cooled by the addition of crushed ice and made alkaline with aqueous ammonia. The mixture was extracted with ether, the ethereal extract dried (K_2CO_3), and the ether removed by distillation. The excess of ethyl *iso*nicotinate was distilled off under reduced pressure and the residue partly distilled and partly sublimed to give a mixture of bases (4·3 g.; b. p. 160—180°/7 × 10^{-3} mm.). On crystallisation from acetone 3-hydroxyquinoline (2·9 g.) separated in cubic crystals, m. p. 190°, and further crystallisation raised the melting point to 196°. Mills and Watson (*J.*, 1910, **97**, 741) record m. p. 198° for 3-hydroxyquinoline. Removal of the acetone from the original mother-liquors left an oil and a further quantity of 3-hydroxyquinoline. The oil was removed from the crystalline solid by trituration with alcohol. After the addition of potassium hydroxide (1 g.) to the alcoholic extracts the mixture was boiled under reflux for two hours. On cooling, the potassium salt of 2-3′-quinolylisonicotinic acid (0·5 g.) separated, and a further quantity was obtained from the mother-liquors. The potassium salt was dissolved in the minimum quantity of water and the free acid liberated by the addition of acetic acid. The acid was purified by dissolving it in aqueous sodium carbonate and stirring with animal charcoal. Acidification of the colourless filtrate with acetic acid gave *2-3′-quinolylisonicotinic acid* as a white flocculent precipitate, which crystallised from dioxan in fine needles, m. p. 260° (Found: C, 72·0; H, 3·9. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0%). No trace of a second isomeride could be detected.

3-2′-Pyridylquinoline.—2-3′-Quinolylisonicotinic acid (0·4 g.) was ground with soda-lime (1 g.) and the mixture dried in an air-oven at 120° for two hours and then strongly heated in a Pyrex tube. 3-2′-Pyridylquinoline distilled from the mixture and, after recrystallisation from light petroleum (b. p. 60—80°) containing a trace of benzene, melted at 99° (Found: N, 13·1. Calc. for $C_{14}H_{10}N_2$: N, 13·6%). No depression in melting point was observed when this compound was mixed with a specimen of 3-2′-pyridylquinoline prepared by the method of Coates *et al.* (*loc. cit.*).

Thanks are due to Professor G. R. Clemo, F.R.S., for providing experimental details for the preparation of ethyl 2-pyridylacetate from the oxime of 2-phenacylpyridine. One of us (J. M. W.) also thanks the South African Council for Industrial and Scientific Research for the award of a Post-M.Sc. Research Bursary held during the present investigation.

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340. *The Preparation of α-Substituted Glutaric Acids.*

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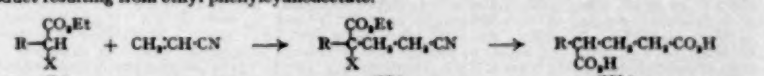
A new general method for the preparation of α-substituted glutaric acids is described. The action of acrylonitrile on a substituted malonic ester or on a substituted cyanoacetic ester gives a cyano-dicarboxylic ester or a dicyano-carboxylic ester respectively, and subsequent hydrolysis and decarboxylation yield an α-substituted glutaric acid. The method is illustrated by the preparation of fourteen such acids, many of which are described for the first time.

ONE of the general methods for the preparation of α-substituted glutaric acids, a series of which was required for another investigation, consists of the condensation of an ethyl β-halogenopropionate with the sodio-derivative of a monosubstituted malonic ester, cyanoacetic ester, or acetoacetic ester, followed by hydrolysis and, in the first two cases, decarboxylation. This method has been used for the preparation of α-methylglutaric acid (Auwers and Titherley, *Annalen*, 1896, **292**, 209; Ingold, *J.*, 1925, 392), α-ethylglutaric acid (Auwers, *Annalen*, 1896, **292**, 144; Berner and Leonardsen, *ibid.*, 1939, **538**, 39), α-*iso*propylglutaric acid (Heinke and Perkin, *J.*, 1896, **69**, 1507; Arne Fredga, *Arkiv Kemi, Min., Geol.*, 1946, **23**, *B*, No. 2), α-phenylglutaric acid (Fichter and Merckens, *Ber.*, 1901, **34**, 4175), and α-benzylglutaric acid (Braun and Manz, *Annalen*, 1929, **468**, 258). Mellor (*J.*, 1901, **79**, 128) adopted a slightly modified procedure in which he condensed the ethyl β-halogenopropionate with ethyl malonate and alkylated the product. Using this method he prepared α-*n*-propylglutaric acid. An alternative procedure utilises the Michael reaction between the ethyl ester of an α-substituted acrylic acid and ethyl malonate, ethyl cyanoacetate, or ethyl acetoacetate, followed by hydrolysis and, in the first two cases, decarboxylation. Thus, Perkin (*J.*, 1896, **69**, 1490) condensed ethyl malonate with ethyl α-*iso*propylacrylate and then hydrolysed and decarboxylated the resulting ethyl α-*iso*propyl-γ-carbethoxyglutarate to give α-*iso*propylglutaric acid. This procedure may be modified by condensing ethyl malonate with ethyl acrylate and alkylating the product (Arne Fredga, *loc. cit.*).

A new general method has now been developed for the preparation of α-substituted glutaric acids which has advantages over the older methods both in the simplicity of the process and in the accessibility of the starting materials. This method utilised the reaction between acrylonitrile and the esters of monosubstituted malonic or cyanoacetic acids (I), whereby the 2-cyanoethyl group is introduced into the malonic or cyanoacetic ester (Bruson and Rinner, *J. Amer. Chem. Soc.*, 1943, **65**, 23; Floyd, *ibid.*, 1949, **71**, 1746). Hydrolysis and decarboxylation of the resulting cyanoethylation product (II) yields the α-substituted glutaric acid (III). During the course of this work Horning and Finelli (*ibid.*, p. 3204) reported the preparation of α-phenylglutaric anhydride from the product obtained on the hydrolysis of the cyanoethylation product resulting from ethyl phenylcyanoacetate.



(I.) (II.) (III.)

(X = CN or CO_2Et).

Using this method the following acids (III) have been prepared: α-methyl- (R = Me), α-ethyl- (R = Et), α-*n*-propyl- (R = Pr^n), α-*iso*propyl- (R = Pr^i), α-*n*-butyl- (R = Bu^n), α-phenyl- (R = Ph), α-benzyl- (R = $Ph{\cdot}CH_2$), α-2-phenylethyl- (R = $Ph{\cdot}CH_2{\cdot}CH_2$), α-1-naphthyl- (R = 1-$C_{10}H_7$), α-1-naphthylmethyl- (R = 1-$C_{10}H_7{\cdot}CH_2$), α-(2-1′-naphthylethyl)- (R = 1-$C_{10}H_7{\cdot}CH_2{\cdot}CH_2$), α-2-naphthyl- (R = 2-$C_{10}H_7$), α-2-naphthylmethyl (R = 2-$C_{10}H_7{\cdot}CH_2$), and α-(2-2′-naphthylethyl)-glutaric acid (R = 2-$C_{10}H_7{\cdot}CH_2{\cdot}CH_2$). The initial malonic or cyanoacetic esters were prepared by published methods with the exception of ethyl 2-naphthylmalonate (I; X = CO_2Et, R = 2-$C_{10}H_7$) and 2-2′-naphthylethylmalonate (I; X = CO_2Et; R = 2-$C_{10}H_7{\cdot}CH_2{\cdot}CH_2$). The former was prepared from ethyl oxalate and ethyl 2-naphthyl-

acetate, which gave ethyl 2-naphthyloxaloacetate from which carbon monoxide was eliminated by heating the ester with powdered glass at 175° under reduced pressure. Ethyl 2-2′-naphthylethylmalonate was prepared by the standard method using ethyl malonate and 2-2′-naphthylethyl bromide. In several cases the intermediate cyano-dicarboxylic esters or dicyano-carboxylic esters (II) were isolated in pure form, but in other cases hydrolysis was effected on the crude product.

Experimental.

α-Methylglutaric Acid.—Acrylonitrile (10·6 g.) was added to a stirred solution of ethyl methylmalonate (Weiner, *Org. Synth.*, Coll. Vol. II, p. 279) (34·8 g.) and 30% methanolic potassium hydroxide (1·0 g.) in *tert.*-butyl alcohol (50 g.). The reaction mixture was kept at 30—35° during the addition, and then stirred for a further 3 hours. The solution was neutralised with 2*N*-hydrochloric acid, diluted with water, and extracted with ether. Evaporation of the dried extract left *ethyl methyl-2-cyanoethylmalonate* (44·0 g.), b. p. 110°/0·04 mm. (Found: C, 57·7; H, 7·4; N, 6·4. $C_{11}H_{17}O_4N$ requires C, 58·2; H, 7·5; N, 6·2%). The ester (10·0 g.) was boiled under reflux with 48% hydrobromic acid (140 c.c.) for 8 hours, and the solution then evaporated almost to dryness under reduced pressure. Sufficient water was added to dissolve the ammonium bromide, and the mixture was extracted with ether. Evaporation of the dried extract left α-methylglutaric acid as an oil (6·2 g.), which solidified when kept. Recrystallisation from benzene gave the pure acid in small needles, m. p. 77—78°. Auwers (*loc. cit.*) records m. p. 77—78° for this acid.

α-Ethylglutaric Acid.—Ethyl ethyl-2-cyanoethylmalonate (5·0 g.), prepared by the method of Bruson and Riener (*loc. cit.*) using *tert.*-butyl alcohol in place of dioxan and 30% methanolic potassium hydroxide in place of trimethylbenzylammonium hydroxide, was hydrolysed by boiling it under reflux with 48% hydrobromic acid (20 c.c.) for 8 hours. The reaction mixture was extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left α-ethylglutaric acid (3·0 g.) as an oil, which when cooled and scratched solidified. Recrystallisation from ice-cold benzene–light petroleum (b. p. 40—60°) gave the pure acid, m. p. 58—60°. Berner and Leonardsen (*loc. cit.*) record m. p. 60—61°.

α-n-Propylglutaric Acid.—*Ethyl n-propyl-2-cyanoethylmalonate* (18·5 g.) was prepared as was ethyl methyl-2-cyanoethylmalonate from ethyl α-propylmalonate (15·1 g.) (Backer and Toxopeus, *Rec. Trav. chim.*, 1926, **45**, 895), acrylonitrile (4·0 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). It separated from ice-cold alcohol in colourless prisms, m. p. 31—32° (Found: C, 61·7; H, 8·1. $C_{12}H_{19}O_4N$ requires C, 61·2; H, 8·2%). This ester (5·0 g.) was hydrolysed by boiling it under reflux with 48% hydrobromic acid (20 c.c.) for 8 hours. The reaction mixture was then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left α-α-propylglutaric acid (3·6 g.) as an oil, which readily solidified. Recrystallisation from water gave the pure acid in small colourless needles, m. p. 69·5—70·5°. Mellor (*loc. cit.*) records m. p. 66—68°.

α-isoPropylglutaric Acid.—*Ethyl isopropyl-2-cyanoethylcyanoacetate* (40·2 g.), b. p. 125°/0·035 mm., was prepared as for ethyl methyl-2-cyanoethylmalonate from ethyl isopropylcyanoacetate (31·0 g.), acrylonitrile (10·6 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (1·0 g.) (Found: C, 63·8; H, 7·8; N, 13·6. $C_{11}H_{16}O_2N_2$ requires C, 63·5; H, 7·7; N, 13·6%). It (10·0 g.) was hydrolysed by boiling 48% hydrobromic acid (40 c.c.) (8 hours), and the reaction mixture then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left α-*iso*propylglutaric acid (5·1 g.) as an oil, which readily solidified. Recrystallisation from water gave the pure acid as small colourless needles, m. p. 94—95°. Perkin (*J.*, 1896, **69**, 1495) records m. p. 94—95°.

α-n-Butylglutaric Acid.—Ethyl α-butyl-2-cyanoethylmalonate (10 g.), prepared by the method of Bruson and Riener (*loc. cit.*) using *tert.*-butyl alcohol and 30% methanolic potassium hydroxide in place of dioxan and trimethylbenzylammonium hydroxide, was hydrolysed by boiling 48% hydrobromic acid (40 c.c.) (8 hours), and the reaction mixture was then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left *α-n-butylglutaric acid* (5·9 g.) as an oil which solidified on storage in an evacuated desiccator over sulphuric acid for several days. Recrystallisation from benzene gave the pure acid, m. p. 40° (Found: C, 57·2; H, 8·4. $C_9H_{16}O_4$ requires C, 57·4; H, 8·5%).

α-Phenylglutaric Acid.—*Ethyl phenyl-2-cyanoethylmalonate* was prepared as for ethyl methyl-2-cyanoethylmalonate from ethyl phenylmalonate (23·6 g.), acrylonitrile (5·3 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left the ester (26·2 g.) as an oil, which when cooled and scratched solidified. Recrystallisation from ice-cold alcohol gave the pure compound as colourless prisms, m. p. 37° (Found: C, 66·6; H, 6·2. $C_{14}H_{15}O_4N$ requires C, 66·4; H, 6·2%). It (19·5 g.) was hydrolysed and worked up as above, α-phenylglutaric acid being obtained (13·8 g.) as an oil, which on storage with occasional cooling and scratching solidified. Recrystallisation from ice-cold benzene–light petroleum (b. p. 40—60°) gave the pure acid in small colourless needles, m. p. 82—84°. Fichter and Merckens (*loc. cit.*) record m. p. 82°.

α-Benzylglutaric Acid.—Ethyl benzylmalonate (Marvel, *Org. Synth.*, 1941, **21**, 99) was condensed with acrylonitrile according to the procedure of Bruson (*loc. cit.*), using *tert.*-butyl alcohol and 30% methanolic potassium hydroxide in place of dioxan and trimethylbenzylammonium hydroxide. The resulting ethyl benzyl-2-cyanoethylmalonate (17·5 g.) was hydrolysed by boiling it under reflux with 48% hydrobromic acid (120 c.c.) for 8 hours and then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left α-benzylglutaric acid (18·2 g.) as an oil, which readily solidified. Recrystallisation from benzene gave the pure acid in small colourless needles, m. p. 77—78°. Braun and Manz (*loc. cit.*) record m. p. 76°.

α-(2-Phenylethyl)glutaric Acid.—Ethyl 2-phenylethyl-2′-cyanoethylmalonate was prepared, as for ethyl methyl-2-cyanoethylmalonate, from ethyl 2-phenylethylmalonate (71·7 g.) (Rupe, *Annalen*, 1913, **395**, 114), acrylonitrile (14·5 g.), *tert.*-butyl alcohol (100 g.), and 30% methanolic potassium hydroxide (5·0 g.). Evaporation of the ethereal extract left the malonate (83·2 g.) as a viscous liquid, b. p. 168—170°/0·03 mm. This compound (30·0 g.), hydrolysed as above, gave *α-(2-phenylethyl)glutaric acid*

(21·3 g.) as an oil, which readily solidified. Recrystallisation from benzene gave the pure acid in small colourless needles, m. p. 86—87° (Found: C, 66·6; H, 6·7. $C_{18}H_{16}O_4$ requires C, 66·7; H, 6·8%).

α-1-Naphthylglutaric Acid.—*Ethyl 1-naphthyl-2′-cyanoethylmalonate* was prepared as above from ethyl 1-naphthylmalonate (21·4 g.) (Blicke and Feldkamp, *J. Amer. Chem. Soc.*, 1944, **66**, 1088), acrylonitrile (4·0 g.), *tert.*-butyl alcohol (75 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left the malonate (22·7 g.) as an oil, which when scratched with ice-cold light petroleum (b. p. 40—60°) solidified. Recrystallisation from alcohol gave the pure compound in colourless prisms, m. p. 82·5—83·5° (Found: C, 70·6; H, 6·1. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2%). This ester (23·0 g.) was hydrolysed by boiling it under reflux with potassium hydroxide (23·0 g.) in alcohol (23 c.c.) and water (18 c.c.). After about 2 hours a considerable amount of solid had separated and water (15 c.c.) was added. Boiling under reflux was continued for a further 4 hours, and the alcohol then distilled off. The residual solution was cooled, diluted with water, and extracted with ether, and the aqueous layer acidified and extracted with ether again. Evaporation of the dried ethereal extract left α-carboxy-α-1-naphthylglutaric acid as an oil, which was decarboxylated by heating at 180—185° for 1 hour (bath-temperature). After cooling, the product was boiled with water for 15 minutes and extracted with ether. Evaporation of the dried ethereal solution left *α-1-naphthylglutaric acid* (16·1 g.) as an oil, which readily solidified. Recrystallisation from benzene–light petroleum (b. p. 40—60°) gave the pure acid in small needles, m. p. 122—124° (Found: C, 70·1; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

α-(1-Naphthylmethyl)glutaric Acid.—Ethyl 1-naphthylmethyl-2′-cyanoethylmalonate was prepared as above from ethyl 1-naphthylmethylmalonate (30 g.) (Fieser and Gates, *J. Amer. Chem. Soc.*, 1940, **62**, 2338), acrylonitrile (5·3 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left ethyl 1-naphthylmethyl-2′-cyanoethylmalonate (33·3 g.) as a viscous liquid, b. p. 156—158°/0·003 mm. This (57·0 g.) was hydrolysed by boiling it under reflux with potassium hydroxide (57 g.) in alcohol (57 c.c.) and water (48 c.c.). Treatment as in the preceding case then gave *α-1-naphthylmethylglutaric acid* (37·5 g.) as an oil, which readily solidified. Recrystallisation from toluene gave the pure acid in small needles, m. p. 144—146° (Found: C, 70·6; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

α-(2-1′-Naphthylethyl)glutaric Acid.—Ethyl 2-1′-naphthylethyl-2″-cyanoethylmalonate was prepared as above from ethyl 2-1′-naphthylethylmalonate (34·5 g.) (Bachmann, Gregg, and Pratt, *J. Amer. Chem. Soc.*, 1943, **65**, 2314), acrylonitrile (6·0 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left the ether (38·1 g.) as a viscous liquid. It (10·2 g.) was hydrolysed with a boiling solution of potassium hydroxide (10·0 g.) in alcohol (10 c.c.) and water (8 c.c.). The reaction product was extracted and decarboxylated as for α-1-naphthylglutaric acid. The decarboxylated product solidified when boiled with water and was filtered off. Recrystallisation from ethyl acetate–benzene (equal volumes) gave *α-(2-1′-naphthylethyl)glutaric acid* (6·5 g.) in small needles, m. p. 171—173° (Found: C, 71·2; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

α-2-Naphthylglutaric Acid.—Ethyl oxalate (19·0 g.) was added to a stirred solution of sodium ethoxide, prepared from absolute alcohol (60 c.c.) and sodium (3·0 g.), followed after a few minutes' stirring by ethyl 2-naphthylacetate (28·8 g.) (Wislicenus and Elvert, *Ber.*, 1916, **49**, 2827) in absolute alcohol (20 c.c.). The solution was heated under reflux for 30 minutes, solid beginning to separate. The mixture was then cooled to 0°, the solid product removed from the flask with the aid of ether, filtered off, washed with ether, and then mixed with water (200 c.c.). When most of it had dissolved, ether (100 c.c.) was added and the solution made just acid to litmus with 20% sulphuric acid. The ethereal layer was separated and the aqueous layer extracted with ether. After the removal of the ether from the dried extracts (Na_2SO_4) the residue of ethyl 2-naphthyloxaloacetate was mixed with powdered glass (4·0 g.) and heated under 15 mm. pressure until the bath temperature reached 175°, where it was kept for 1 hour, after which time evolution of carbon monoxide had ceased. It was then distilled to give *ethyl 2-naphthylmalonate* (16·0 g.), b. p. 168—172°/0·5 mm., which immediately solidified. Recrystallisation from light petroleum (b. p. 60—80°) gave the pure ester in stout needles, m. p. 99—100° (Found: C, 71·1; H, 6·0. $C_{15}H_{16}O_4$ requires C, 71·3; H, 6·3%). The ethyl 2-naphthylmalonate (5·0 g.) was dissolved in *tert.*-butyl alcohol (20 g.) with heating, and the solution then cooled with stirring to 30°, thus yielding a fine suspension. 30% Methanolic potassium hydroxide (1·0 g.) was added, followed by acrylonitrile (2·0 g.). The ethyl 2-naphthylmalonate dissolved and the temperature of the solution rose and was allowed to reach a maximum of 40°. After a further 3 hours' stirring, the solution was extracted as for ethyl methyl-2-cyanoethylmalonate. Evaporation of the ethereal extract left ethyl 2-naphthyl-2-cyanoethylmalonate (5·5 g.) as a viscous liquid, b. p. 170—175°/0·03 mm. This compound (4·5 g.) was hydrolysed by boiling it under reflux with a solution of potassium hydroxide (4·5 g.) in alcohol (5 c.c.) and water (5 c.c.). After about 2 hours a considerable amount of solid had separated and water (5 c.c.) was added, and heating continued for a further 4 hours. The reaction product was then extracted as for α-1-naphthylglutaric acid. After boiling of the decarboxylated product with water the oily acid solidified on cooling and was filtered off. Recrystallisation from water gave *α-2-naphthylglutaric acid* (3·0 g.) in small needles, m. p. 109—110° (Found: C, 69·6; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

α-(2-Naphthylmethyl)glutaric Acid.—Ethyl 2-naphthylmethyl-2′-cyanoethylmalonate was prepared as above from ethyl 2-naphthylmethylmalonate (27·6 g.) (Mayer and Sieglitz, *Ber.*, 1922, **55**, 1855), acrylonitrile (4·9 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left ethyl 2-naphthylmethyl-2′-cyanoethylmalonate (30·8 g.). The ester (28·0 g.) was hydrolysed by a boiling solution of potassium hydroxide (28·0 g.) in alcohol (28 c.c.) and water (23 c.c.) (6 hours). The reaction product was then extracted and decarboxylated as for α-1-naphthylglutaric acid. Evaporation of the ethereal extract left *α-(2-naphthylmethyl)glutaric acid* (27·6 g.) as an oil which readily solidified. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the pure acid in small needles, m. p. 124—125° (Found: C, 70·9; H, 5·7. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

α-(2-2′-Naphthylethyl)glutaric Acid.—Absolute alcohol (37 c.c.) was added slowly to a suspension of powdered sodium (3·5 g.) in dry benzene (11 c.c.). After the mixture had been heated under reflux

for a short time all the sodium had reacted, and ethyl malonate (37 c.c.) was added, followed after 30 minutes' heating by 2-2′-naphthylethyl bromide (25·0 g.) (Karrer, Geiger, Ruegger, and Schwab, *Helv. Chim. Acta*, 1940, **23**, 586) in benzene (40 c.c.). The reaction mixture was kept warm on a water-bath overnight and then boiled under reflux for 1½ hours. After cooling the mixture was diluted with water and neutralised with 2*N*-hydrochloric acid, the benzene layer separated, and the aqueous layer extracted with ether. After drying of the combined extracts (Na_2SO_4), the solvents were removed and the residual oil was distilled to give ethyl malonate (14·6 g.), b. p. 85—88°/10 mm., and *ethyl 2-2′-naphthylethylmalonate* (28·5 g.), b. p. 197—202°/0·2 mm. (Found: C, 72·0; H, 7·4. $C_{19}H_{24}O_4$ requires C, 72·6; H, 7·6%). This ester (25·0 g.) was condensed with acrylonitrile (4·2 g.) in *tert.*-butyl alcohol (50 g.) in the presence of 30% methanolic potassium hydroxide (2·0 g.) as for ethyl methyl-2-cyanoethylmalonate. Evaporation of the ethereal extract gave ethyl 2-2′-naphthylethyl-2″-cyanoethylmalonate (28·0 g.) as a viscous liquid. The latter compound (28·0 g.) was hydrolysed by heating it under reflux with potassium hydroxide (28·0 g.) in alcohol (28 c.c.) and water (28 c.c.) for 6 hours. The reaction product was extracted as for α-1-naphthylglutaric acid. Evaporation of the ethereal extract gave a solid which was decarboxylated at 200—205° (bath-temperature) (45 minutes). After cooling, it was boiled with water for 15 minutes and extracted with ether. Evaporation of the dried ethereal solution gave *α-(2-2′-naphthylethyl)glutaric acid* (19·9 g.) as an oil, which readily solidified. Recrystallisation from benzene gave the pure acid in small needles, m. p. 117—119° (Found: C, 71·3; H, 6·4. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

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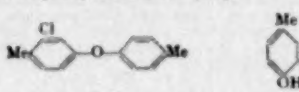
341. *Reactions of Halogens with Phenols.*

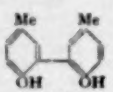
By K. BOWDEN and C. H. REECE.

Chlorine or sulphuryl chloride with *p*-cresol at room temperature gives, besides chlorocresols, the ether (I) and the di- and ter-phenyl derivatives (II) and (III). The general applicability of the reaction to a variety of phenols and to bromine has been examined and a possible mechanism put forward to account for the formation of these compounds.

THE reaction of halogens with phenols under mild conditions has long been known to yield simple halogen-substituted phenols. The present investigations have shown that chlorine or chlorine-generating compounds can give, from some phenols, a variety of more unusual products under these conditions. Thus sulphuryl chloride or chlorine gives with *p*-cresol, not only 3-chloro-*p*-cresol, but also 3-chloro-4 : 4′-dimethyldiphenyl ether (I), the diphenyl derivative (II), and the terphenyl derivative (III).



(I.)



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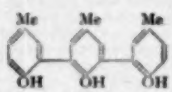


(III.)

The general procedure adopted for the preparation of these types of compounds is reaction with sulphuryl chloride at 20—30° in the presence of a small amount of zinc chloride. Although zinc chloride is not essential for the reaction, better yields are obtained in its presence: the combined yields of (I)—(III) from *p*-cresol approximate to 26%, and that of 3-chloro-*p*-cresol to 13%.

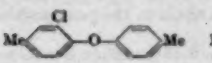
The formation of compounds (I)—(III) appears to be little affected by temperature over the range investigated (20—100°), and variation in the molecular ratio of sulphuryl chloride to *p*-cresol alters mainly the ratio to each other in which these compounds are formed and not their combined yields (see Table, p. 1689).

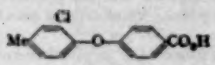
Distillation of the *p*-cresol reaction mixture, after removal of zinc salts, gave four fractions, (*A*)—(*D*).

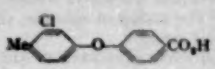
The first, (*A*), consisted of unchanged *p*-cresol and chlorocresol which were separated by distillation of their methyl ethers.

Fraction (*B*) had the empirical formula $C_{14}H_{13}OCl$, gave no colour with ferric chloride solution, and was insoluble in dilute sodium hydroxide. It was recovered almost quantitatively after being refluxed with 20% alcoholic potash or hydrogen iodide. It is thus probably the ditolyl ether (I) or (IV) with the halogen in the nucleus. It did not yield a picrate and decomposed on attempted nitration with fuming nitric acid in sulphuric acid at 0° [Reilly,

Drumm, and Barrett (*J.*, 1927, 67) obtained a similar result when they attempted to nitrate di-*p*-tolyl ether]. Oxidation by potassium permanganate in aqueous pyridine gave a monocarboxylic acid which did not melt below 300° and which gave an *S*-benzylthiuronium salt, m. p. 184°. The ethers (I) and (IV) were synthesised and oxidised to their respective acids (V) and (VI). The acid from fraction (*B*) was unexpectedly found to have the structure (VI).


(IV.)


(V.)


(VI.)

(VII.)

The only chloro-4 : 4′-dimethylphenyl ether recorded in the literature is that obtained by chlorinating 4 : 4′-dimethyldiphenyl ether, when the halogen was thought to enter position 2, giving (IV) (Mailhe and Murat, *Bull. Soc. chim.*, 1912, [iv], **11**, 288). Chlorination of di-*p*-tolyl ether with sulphuryl chloride in the presence of iodine gave an oil, b. p. 311—314°/758 mm., which was identical with the chlorodimethyldiphenyl ether obtained from 2-amino-4 : 4′-dimethyldiphenyl ether by a Sandmeyer reaction and therefore had the structure (IV). Oxidation of this ether gave the carboxylic acid (V), characterised as its *S*-benzylthiuronium salt.

The ether (IV) was also prepared from the potassium salt of 3-chloro-*p*-cresol and *p*-bromotoluene. This general method of preparing chloroditolyl ethers was found to be satisfactory for preparation of (I) from 2-chloro-*p*-cresol and *p*-bromotoluene after other syntheses had failed.

Fraction (*C*) after crystallisation had m. p. 154°, was soluble in dilute sodium hydroxide solution, and gave a greenish-blue colour with dilute ferric chloride solution. It had the empirical formula C_7H_8O and gave a crystalline benzoate and acetate. It was identical with the diphenyl derivative (II) obtained by Pummerer *et al.* (*Ber.*, 1922, **55**, 3116) and by Westerfield and Lowe (*J. Biol. Chem.*, 1942, **145**, 463) by different processes, and differed from the isomer (VII) in its ultra-violet absorption spectrum.

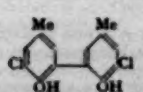
Fraction (*D*) after crystallisation had m. p. 197°. It was a phenol, of formula $C_{21}H_{20}O_2$. It has been recorded by Pummerer *et al.* and by Westerfield and Lowe (*locc. cit.*), the latter authors concluding that it was the terphenyl derivative (III).

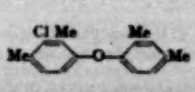
The compounds (II) and (III) were obtained from *p*-cresol by potassium ferricyanide (Pummerer *et al.*) and the enzyme peroxidase (Westerfield and Lowe) and could conceivably have been formed by free-radical mechanisms (see Harington, *J.*, 1944, 193). Our investigations of the reaction between sulphuryl chloride and *p*-cresol preclude free-radical mechanisms. The presence of sulphur or organic nitro-compounds, known to inhibit free-radical mechanisms (Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2142), did not influence the course of the reaction to any large extent (see Table). Again, the addition of benzoyl peroxide, known to promote the formation of free radicals, had no influence. This, and the unexpected configuration of the product (I), having the chloro-group in position 3 and not the expected position 2, indicated that the halogen atom had not been introduced by simple substitution into either *p*-cresol or 4 : 4′-ditolyl ether, and led us to consider mechanisms other than those involving free radicals to explain the formation of all three types of product.

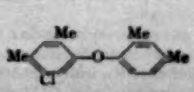
When chlorine was passed into *p*-cresol in the presence of a trace of zinc chloride the same products were formed as when sulphuryl chloride was used, showing that the sulphuryl chloride was acting solely as a source of molecular chlorine.

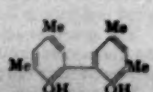
From 3-chloro-*p*-cresol, sulphuryl chloride in the presence of a small amount of zinc chloride gave a 13·7% yield of 3 : 5-dichloro-*p*-cresol and a 9·6% yield of 3 : 3′-dichloro-2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (VIII). In this experiment less than 1% of the expected ether (XIV) was formed.

From *m*-4-xylenol, an ether, presumably (IX) or (X), was formed in 4·7% yield, together with a dihydroxytetramethyldiphenyl (XI) (cf. Bamberger and Brun, *Ber.*, 1907, **40**, 1952).


(VIII.)


(IX.)


(X.)


(XI.)

On the other hand phenol, *o*- and *m*-cresols, *p*-*tert*.-butylphenol, and *p*-tolyl methyl ether

with sulphuryl chloride and zinc chloride gave only simple chlorinated derivatives, and 3 : 5-dichloro- and 3-nitro-*p*-cresol did not react.

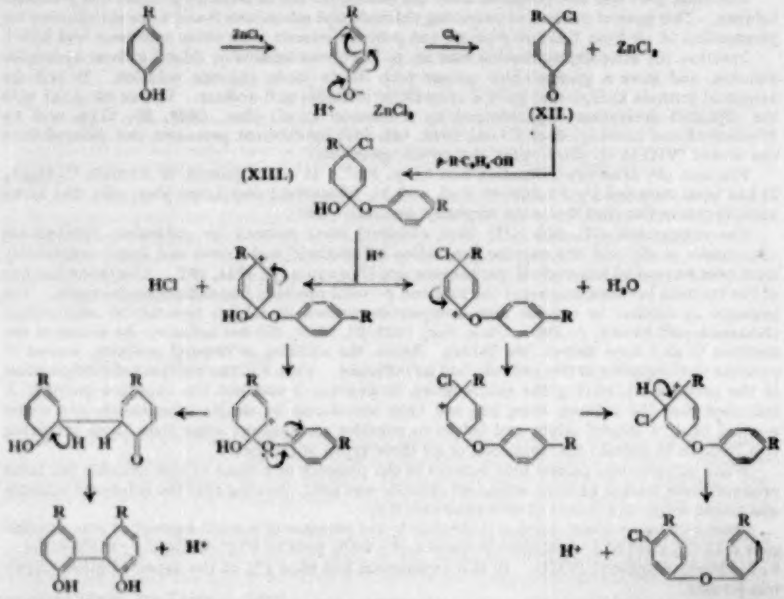
Either bromine or *N*-bromosuccinimide with *p*-cresol in the presence of the same catalyst gave only simple bromocresols and hydrogen chloride was without effect on a mixture of *p*-cresol and zinc chloride.

Discussion.—From the above results it appears that for products of the type (I)—(III) to be produced by the action of chlorine, the phenol must have a side chain in the *para*-position to a free hydroxyl group.

The negligible effect of substances which promote or inhibit free-radical formation is evidence against the products being formed by free-radical mechanisms. Again the possibility of the reactions proceeding *via* the derived *p*-methylene-quinones was discounted in view of the readiness with which such compounds react with hydrochloric acid (which is produced in large amounts during the reaction) to give *p*-hydroxybenzyl chlorides.

From the experimental results obtained the mechanism shown in the chart seems to be the most suitable hypothesis. Repetition of the process giving diphenyl derivatives will obviously give ter- and poly-phenyl derivatives.

This hypothesis explains (see Table) why only small amounts of zinc chloride are necessary; also why copper and cobalt chlorides do not act as catalysts, since their affinity for electrons is much less than that of aluminium chloride, zinc chloride, or sulphur dichloride (formed from



sulphur when it was added to the reaction mixture). It can be seen that according to this mechanism the reaction will proceed in the absence of a catalyst but the yields will be decreased as the molecule is less activated.

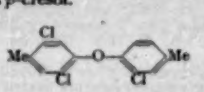
The non-formation of compounds similar to (XII) from phenol or *o*- or *m*-cresol explains why they yield only mononuclear chlorinated products. In the case of *tert.*-butylphenol it is considered that the reaction is sterically hindered.

The mechanism also explains why 3-chloro-*p*-cresol gives so much less of the ether (XIV) than of the diphenyl derivative (VIII); for, although the halogen atom in 3-chloro-*p*-cresol tends to deactivate the whole ring, it has a greater effect on adjacent position than on others,

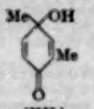
Effects of various reagents and conditions on the reaction between sulphuryl chloride and p-cresol (21 g.).

Mol. ratio, SO_2Cl_2/*p*-cresol.	Temp.	Catalyst.	Yields, mol.-%. (I.)	(II.)	(III.)
1 : 2	30°	$ZnCl_2$, 2 g.	5·5	16·8	3·8
,,	,,	Nil	1·5	4·6	—
,,	100	$ZnCl_2$, 2 g.	5·6	15·1	3·7
,,	,,	$ZnCl_2$, 28 g.	6·0	16·8	3·6
,,	30	$ZnCl_2$, 2 g. + Bz_2O_2, 0·5 g.	5·6	16·8	2·9
1 : 1	,,	$ZnCl_2$, 2 g.	6·0	11·5	8·5
1 : 2	,,	$CoCl_2$, 2 g.	0·9	3·2	—
,,	,,	Cu_2Cl_2, 2 g.	1·3	3·6	—
,,	,,	$AlCl_3$, 2 g.	11·5	8·0	—
,,	,,	S, 2 g.	4·8	15·5	2·8
,,	,,	$Ph{\cdot}NO_2$, 2 c.c.	0·9	3·2	—
,,	,,	$ZnCl_2$, 2 g. + $Ph{\cdot}NO_2$, 25 c.c.	4·9	17·4	3·8

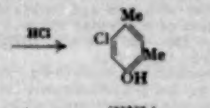
so that in the intermediate (XIII) the affinity of the hydroxyl group for the hydrogen ion is decreased more than is that of the halogen in the *para*-position. Therefore only (VIII) is obtained in any quantity, although the yield of this is less than that of the corresponding ether obtained from *p*-cresol.



(XIV.)



(XV.)



(XVI.)

The aromatic ring of 3-nitro- or 3 : 5-dichloro-*p*-cresol is deactivated to such an extent as to prevent the formation of compounds similar to (XII).

From the above hypothesis it can be deduced that the chloro-ether obtained from *m*-4-xylenol and sulphuryl chloride has the structure (X) since Bamberger and Reber (*Ber.*, 1907, **40**, 2268) obtained 6-chloro-*m*-4-xylenol (XVI) by heating *m*-xylene-ϕ-quinol (XV) with hydrogen chloride.

Experimental.

(Analyses by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

Reaction of Sulphuryl Chloride with p-*Cresol in the Presence of Zinc Chloride.*—Sulphuryl chloride (13·5 g.) was added during 45 minutes to a stirred mixture of *p*-cresol (21·0 g.) and powdered anhydrous zinc chloride (2·0 g.) starting at 30°, at which temperature the mixture is liquid. During the addition the temperature fell to 20°, the mixture remaining liquid. After about 20 minutes hydrogen chloride and sulphur dioxide were evolved and the temperature rose to 25°, the mixture darkening and the zinc chloride slowly dissolving. The mixture was stirred at room temperature overnight and then shaken with water and light petroleum (b. p. 60—80°). The light petroleum layer, after being dried (Na_2SO_4), was distilled to give the following fractions: (*A*) b. p. 94—97°/15 mm. (15·8 g.), (*B*) b. p. 110—120° (air-bath temp.)/2 × 10^{-4} mm. (1·28 g.), (*C*) b. p. 160—175° (air-bath temp.)/2 × 10^{-4} mm. (3·67 g.), and (*D*) b. p. 200—220° (air-bath temp.)/2 × 10^{-4} mm. (0·78 g.). The higher-boiling residue (1·3 g.) was not investigated.

Fraction (A). The total fraction, dissolved in a solution of sodium hydroxide (6·0 g.) in water (30 c.c.), was cooled to 5° and methylated with methyl sulphate (20 g.) (stirring) at that temperature for 2 hours and then at the b. p. for 2 hours. The resulting ethers were fractionally distilled giving *p*-tolyl methyl ether, b. p. 172—177°/748 mm. (11·3 g.), followed by an intermediate fraction, b. p. 177—212°/748 mm. (0·9 g.), and 3-chloro-*p*-tolyl methyl ether b. p. 212—217°/748 mm. (4·0 g.).

Fraction (B). This was a colourless oil, b. p. 133—136°/0·1 mm., m. p. 17°, sparingly soluble in aqueous alcohol (Found: C, 72·6; H, 5·4; Cl, 16·1%; *M*, 205. $C_{15}H_{15}OCl$ requires C, 72·2; H, 5·6; Cl, 15·2%; *M*, 232).

To the oil (0·6 g.) and water (3 c.c.), pyridine was added until a homogeneous solution was formed. Potassium permanganate (1·7 g.) was added and the stirred solution heated on the steam-bath for 1 hour. After filtration hot, the filtrates were decolorised with sulphur dioxide and acidified with hydrochloric acid, to give a precipitate (0·52 g.) which was dissolved in hot 5% sodium hydroxide solution (4·0 c.c.) and allowed to cool, to give white needles of the sodium salt of the carboxylic acid. These were filtered off and then dissolved in hot water, and the carboxylic acid was precipitated as a white solid by hydrochloric acid. *p-Carboxyphenyl 2-chloro-p-tolyl ether* (VI), crystallised from glacial acetic acid, had m. p. >300° (0·32 g.) (Found: C, 64·1; H, 4·5; Cl, 13·5. $C_{14}H_{11}O_3Cl$ requires C, 64·2; H, 4·2; Cl, 13·1%). Acidification of the alkaline filtrates from the crystallisation of the sodium salt gave material which was probably a mixture of mono- and di-carboxylic acids. The *S-benzylisothiuronium* salt of the carboxylic acid crystallised from aqueous alcohol as colourless rosettes, m. p. 184° (Found: C, 62·6; H, 5·1. $C_{36}H_{34}O_6N_4ClS$ requires C, 62·2; H, 4·9%).

Fraction (C). The crude material had m. p. 156°. It crystallised as a colourless solid, m. p. 154°, from *cyclo*hexane (Found: C, 79·7; H, 6·4. Calc. for $C_{15}H_{14}O_2$: C, 79·6; H, 6·2%). Light absorption:

Max. at 2930 A.; $\epsilon = 8200$ (alcohol). Westerfield and Lowe (*J. Biol. Chem.*, 1942, **145**, 464) give m. p. 134° for the diphenyl derivative (II), and cite a maximum at 2930 A. ($\epsilon = 6000$). The acetyl derivative had m. p. 88° (Westerfield and Lowe, *loc. cit.*, give m. p. 88°). The *dibenzoate* crystallised from cyclohexane or methyl alcohol in long colourless needles, m. p. 133° (Found: C, 79·2; H, 5·3. $C_{32}H_{26}O_4$ requires C, 79·6; H, 5·3%).

Fraction (D). The crude material had m. p. 194° and crystallised from methyl alcohol–benzene as colourless plates, m. p. 197°. It was soluble in dilute sodium hydroxide and gave a pale green colour with ferric chloride solution (Found: C, 78·5; H, 6·4%; *M*, 306. Calc. for $C_{18}H_{18}O_3$: C, 78·7; H, 6·6%; *M*, 320). Light absorption: Max. at 2930 A.; $\epsilon = 13{,}000$ (alcohol). Westerfield and Lowe (*loc. cit.*) give m. p. 196° for the terphenyl derivative (III) and a maximum at 2950 A. ($\epsilon = 12{,}400$).

Reaction of Chlorine with p-Cresol in the Presence of Zinc Chloride.—Dry chlorine was slowly passed into a mixture of *p*-cresol (21 g.) and finely powdered anhydrous zinc chloride (2 g.) at 30—20° until it had increased by 4 g. The reaction mixture was stirred overnight at room temperature and worked up in the usual manner. After removal of the more volatile fraction the residue was distilled at 2×10^{-4} mm., giving the following fractions: air-bath temp. 110—120°, ditolyl ether (I) (1·2 g.); 160—170°, diphenyl derivative (II), m. p. 153° (2·5 g.); and 200—220°, terphenyl derivative (III), m. p. 197° (1·6 g.).

2-Chloro-4 : 4′-dimethyldiphenyl Ether (IV).—(*a*) Di-*p*-tolyl ether in carbon tetrachloride was chlorinated with sulphuryl chloride at room temperature, giving 2-chloro-4 : 4′-dimethyldiphenyl ether, b. p. 311—314° (42%) (Found: C, 73·0; H, 5·6. Calc. for $C_{14}H_{13}OCl$: C, 72·2; H, 5·6%).

(*b*) 2-Nitro-4 : 4′-dimethyldiphenyl ether was obtained in 42% yield from 4-bromo-3-nitrotoluene and potassium hydroxide in an excess of *p*-cresol at 150—175°, in the presence of a small amount of water (cf. Reilly, Drumm, and Barrett, *J.*, 1927, 67) and was reduced to 2-amino-4 : 4′-dimethyldiphenyl ether with iron and hydrochloric acid (yield, 92%) (cf. Reilly and Barrett, *J.*, 1927, 1309). Diazotisation of the amine followed by a Sandmeyer reaction gave 2-chloro-4 : 4′-dimethyldiphenyl ether, b. p. 130—133°/0·5 mm. (30%) (Found: C, 72·5; H, 5·9; Cl, 14·3. Calc. for $C_{14}H_{13}OCl$: C, 72·2; H, 5·6; Cl, 15·2%).

(*c*) Potassium hydroxide (5·6 g.) was dissolved in 3-chloro-*p*-cresol (29 g.) on the steam-bath. Copper bronze (5 g.) and *p*-bromotoluene (17·1 g.) were added and the stirred mixture heated on a wax-bath to 160°; at this temperature a slight reaction commenced, so the bath was removed until the internal temperature began to fall, the flask being then re-immersed and the temperature raised to 175°. The mixture was stirred at this temperature for 30 minutes and after cooling was shaken with water and ether. The ethereal layer was washed with dilute sodium hydroxide solution, then with water, and dried (Na_2SO_4). The ethereal solution was distilled to give unchanged bromotoluene and later a fraction, b. p. 140—143°/0·8 mm., consisting of an oil containing a little solid. The methanol-soluble material, on distillation at 1 mm. pressure, gave 2-chloro-4 : 4′-dimethyldiphenyl ether, b. p. 143—145° (3·9 g., 17%) (Found: C, 72·3; H, 5·8%).

Oxidation. To the ether (5 g.) and water (30 c.c.) was added pyridine until the mixture became homogeneous. Potassium permanganate (14·2 g.) was added and the solution heated on the steam-bath for 1 hour by which time the pink colour had disappeared. The mixture was filtered hot and the colourless filtrates were acidified with concentrated hydrochloric acid, a white solid being precipitated. This was filtered off and dissolved in hot 8% sodium hydroxide solution (40 c.c.) from which the sodium salt of the carboxylic acid crystallised out on cooling. After filtration, the crystals were dissolved in hot water and the solution was acidified with concentrated hydrochloric acid, giving a white precipitate, which was filtered off and dried (yield, 2·8 g.). *p-Carboxyphenyl 3-chloro-p-tolyl ether* (V) crystallised from dilute acetic acid but did not melt below 300° (Found: C, 64·2; H, 4·1. $C_{14}H_{11}O_3Cl$ requires C, 64·2; H, 4·2%). The *S-benzylisothiuronium* salt crystallised from aqueous methyl alcohol as small needles, m. p. 169° (Found: C, 62·1; H, 4·8. $C_{23}H_{21}O_3N_2ClS$ requires C, 62·2; H, 4·9%).

3-Chloro-4 : 4′-dimethyldiphenyl Ether (I).—Potassium hydroxide (5·6 g.) was dissolved in 2-chloro-*p*-cresol (29 g.) on the steam-bath. Copper bronze (5 g.) and *p*-bromotoluene (17·1 g.) were added and the stirred mixture was treated as in preparation (*c*) of the ether (IV). The resulting ethereal solution was distilled, giving *3-chloro-4 : 4′-dimethyldiphenyl ether*, b. p. 148—151°/1 mm., m. p. 16—17° (9·8 g., 42%) (Found: C, 72·0; H, 6·1; Cl, 15·5%).

Oxidation. The foregoing ether (3 g.) was oxidised with potassium permanganate in aqueous pyridine as was the isomer (IV), and the resulting carboxylic acid was dissolved in hot 5% sodium hydroxide solution (20 c.c.). The sodium salt crystallised on cooling of the mixture and was filtered off and dried (yield, 1·8 g.). The *S*-benzyl*isothiuronium* salt crystallised from aqueous alcohol as colourless needles, m. p. 184°, not depressed on admixture with the salt of the oxidised material obtained by the action of sulphuryl chloride on *p*-cresol.

Reaction of Sulphuryl Chloride with m-4-Xylenol in the Presence of Zinc Chloride.—Sulphuryl chloride (13·5 g.) was added to a stirred mixture of *m*-4-xylenol (24·5 g.) and powdered zinc chloride (2 g.) at 30°. After the mixture had been stirred overnight it was worked up as in the reaction with *p*-cresol. After removal of the lower-boiling phenolic fractions distillation of the residue gave: (*a*) *5-chloro-2 : 4 : 2′ : 4′-tetramethyldiphenyl ether* (X) (1·2 g., 4·7%), a neutral oil, b. p. 110—125° (air-bath temp.)/2×10^{-4} mm. (Found: C, 73·4; H, 6·1; Cl, 13·8. $C_{16}H_{17}OCl$ requires C, 73·7; H, 6·5; Cl, 13·6%); (*b*) the diphenyl derivative (XI) (3·9 g., 16·1%), b. p. 160—175° (air-bath temp.)/2×10^{-4} mm., a colourless oil which solidified on cooling. (XI) crystallised from ligroin in white needles, m. p. 136° (Hamberger and Brun, *Ber.*, 1907, **40**, 1932, give m. p. 137°) (Found: C, 79·0; H, 7·4. Calc. for $C_{16}H_{18}O_2$: C, 78·8; H, 7·2%).

Reaction of Sulphuryl Chloride with 3-Chloro-p-cresol in the Presence of Zinc Chloride.—The chloro-cresol (43 g.) was mixed with powdered anhydrous zinc chloride (2 g.), and sulphuryl chloride (20·5 g.) added to the stirred mixture at 30°. After being stirred overnight the mixture was shaken with water and light petroleum (b. p. 60—80°), and the organic layer extracted with 8% sodium hydroxide solution (200 c.c.) and then dried (Na_2SO_4). After removal of the solvent a yellow oil (0·2 g.), which solidified on cooling and had the characteristic odour of a diphenyl ether, remained.

The sodium hydroxide solution was acidified with concentrated hydrochloric acid and the oily mixture extracted with ether. The ethereal extract was dried (Na_2SO_4) and distilled to give unchanged chlorocresol, b. p. 96—99°/14 mm. (29 g., 67·5%), followed by **3** : 5-dichloro-*p*-cresol, b. p. 120—125°/14 mm. (7·3 g., 13·7%), and **3** : 3′-*dichloro*-2 : 2′-*dihydroxy*-5 : 5′-*dimethyldiphenyl* (VIII), b. p. 165—180° (air-bath temp.)/2 × 10^{-4} mm., as an oil which solidified on cooling and crystallised from *cyclo*hexane in white rosettes, m. p. 136° (4·0 g., 9·6%) (Found : C, 59·4; H, 4·2; Cl, 25·6. $C_{14}H_{12}O_2Cl_2$ requires C, 59·4; H, 4·2; Cl, 25·1%). The *dibenzoate* of (VIII), crystallised from methyl alcohol, had m. p. 140° (Found : C, 68·0; H, 4·1. $C_{28}H_{20}O_4Cl_2$ requires C, 68·4; H, 4·0%).

The authors are indebted to Dr. E. A. Braude for light-absorption data.

THE UNIVERSITY, LEEDS, 2. [*Received, March 17th*, 1950.]

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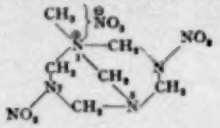
342. *On the Structure of Knudsen's Base and of Related Compounds. Part II.*

By M. E. FOSS, E. L. HIRST, J. K. N. JONES, H. D. SPRINGALL, A. T. THOMAS, and T. URBAŃSKI.

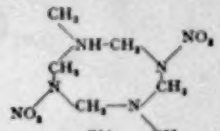
Further evidence is adduced for the identity of the corresponding salts of Knudsen's base, of the base obtained by treating hexamine dinitrate with hot solvents, and of the 1-methylhexamine ammonium cation, from the study of dinitro- and nitrosonitro-derivatives and of dipicrates. The mechanism of the production of the methylhexamine cage is considered.

THE work described in Part I (*J.*, 1950, 624) establishes with reasonable certainty the threefold identity among the corresponding salts of (1) Knudsen's base, (2) the base *A* obtained by treating hexamine dinitrate with hot solvents, and (3) the methylhexamine cation, but some further evidence along three lines is described below.

(1) *Dinitro-derivatives.*—Knudsen's nitrate and authentic hexamine methonitrate were treated with cold nitric acid (98%), a reaction which with the authentic methonitrate has been shown by workers in the University of Pennsylvania to give **3** : 7-dinitro-1-methylpentamethylenetetramine 1-nitrate (IV), m. p. 143° (private communication from Professor Marvin Carmack). According as Knudsen's nitrate has structure (III) or (II) of Part I, it should give either (IV) or **3** : 7-dinitro-1 : 5-dimethyl-1 : 3 : 5 : 7-tetra-aza*cyclo*octane 1-nitrate (V).



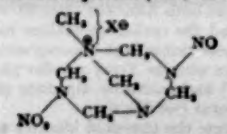
(IV.)



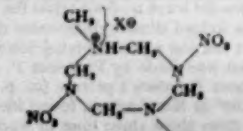
(V.)

Both products had m. p. 142° alone or mixed, and both gave positive Thiele–Lachmann tests for *N*-nitro-groups and negative Liebermann tests for *N*-nitroso-groups. The analytical data (see table), especially the values for *N*-Me and CH_2, confirm the structure (IV) for the products and thus structure (III; X = NO_3, of Part I) for Knudsen's nitrate. The corresponding picrates were also prepared and similarly found to be identical, and to be derived from structure (IV).

(2) *Nitrosonitro-derivatives.*—Knudsen's picrate and authentic hexamine methopicrate were treated with a mixture of nitric acid (98%) and dinitrogen tetroxide. Hexamine methonitrate under these conditions yields 3-nitroso-7-nitro-1-methylpentamethylenetetramine 1-nitrate (VI; X = NO_3) (private communication from Dr. A. Carruthers, then of Bristol University). Hexamine methopicrate would be expected, therefore, to yield (VI; X = picrate), and Knudsen's picrate either (VI; X = picrate) or 3-nitroso-7-nitro-1 : 5-dimethyl-1 : 3 : 5 : 7-tetra-aza*cyclo*octane 1-picrate (VII; X = picrate).



(VI.)



(VII.)

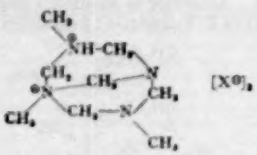
Both the products have m. p. 128—129° alone or mixed, and both give positive Thiele-Lachmann and positive Liebermann tests. This and analyses (see table) indicate that they are identical nitrosonitro-compounds of structure (VI; X = picrate) and confirm the structure (III) for Knudsen's base salts.

		C, %	H, %	N, %	*N*-CH_2, %	CH_2, %	Anion $X^{\ominus}$, %	
Dinitro-nitrate.								
Found	From Knudsen's nitrate	24·7	4·6	33·1	4·0	24·1	21·8	nitrate
	From hexamine methonitrate	24·5	4·5	33·6	4·2	23·6	21·1	
Calc.	For $C_{13}H_{18}O_7N_7$ (IV)	24·4	4·4	33·2	5·1	23·8	21·0	
	For $C_{26}H_{34}O_7N_7$ (V)	24·2	5·0	33·0	10·1	18·8	20·9	
Nitrosonitro-picrate.								
Found	From Knudsen's picrate	32·2	3·3	29·7	3·1	15·6	51·2	picrate
	From hexamine methopicrate	32·6	3·5	27·6	4·5	14·9	50·9	
Calc.	For $C_{13}H_{15}O_{16}N_9$ (VI; X = picrate)	32·4	3·4	29·4	6·5	15·8	51·3	
	For $C_{19}H_{17}O_{16}N_9$ (VII; X = picrate)	32·3	3·8	28·2	13·0	12·5	51·1	
Dipicrate.								
Found	From Knudsen's picrate	38·6	3·6	22·8	6·2	13·1	71·4	
	From hexamine methopicrate	38·5	3·7	22·7	6·4	13·0	71·2	
	Authentic dimethylhexamine dipicrate	38·4	3·8	22·9	6·4	13·4	72·4	
Calc.	For $C_{20}H_{18}O_{14}N_{10}$ (VIII; X = picrate)	38·4	3·6	22·4	9·3	13·4	72·8	
	For $C_{20}H_{18}O_{14}N_{10}$ (IX; X = picrate)	38·2	3·8	22·4	13·8	11·2	72·6	

(3) *Dipicrates.*—The elements of methyl picrate were added to Knudsen's picrate and authentic hexamine methopicrate and the product, in each case, was identified with dimethylhexamine dipicrate, m. p. 212° (VIII; X = picrate), prepared independently *via* the dinitrate in McGill University (private communication from Professor Carl Winkler) from hexamine and methylammonium nitrate and in Bristol University (private communication from Dr. A. Carruthers) from 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane, formaldehyde, ammonium nitrate, and nitric acid.

[$X^{\ominus}$]$_2$

(VIII.)



[$X^{\ominus}$]$_2$

(IX.)

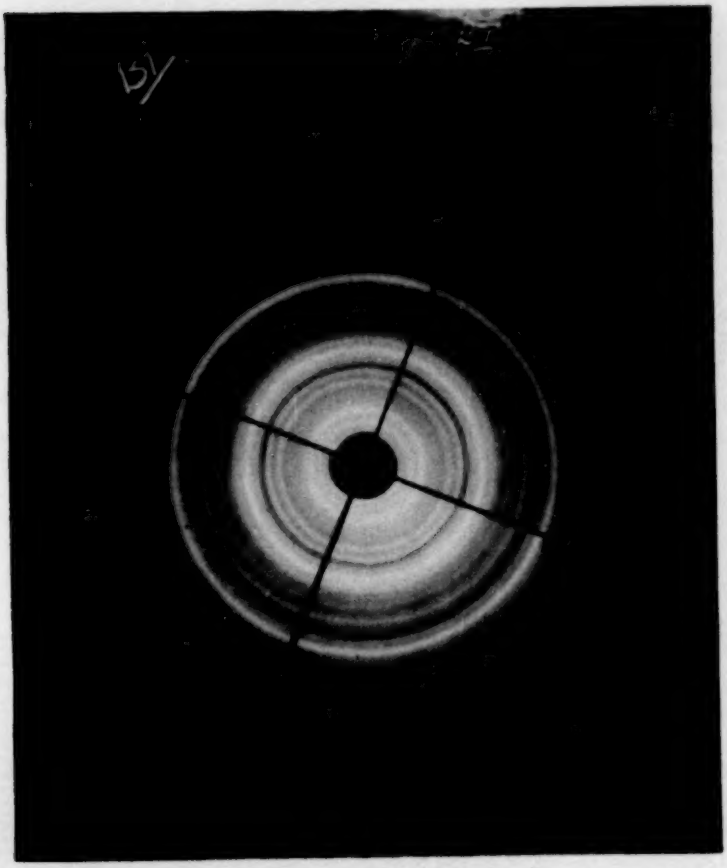
Had Knudsen's picrate had structure (II; X = picrate) of Part I, the product of the addition of methyl picrate would probably have been (IX; X = picrate), differing widely from (VIII) in the significant *N*-methyl and methylene contents. Analytical results are given in the table.

The dipicrates from Knudsen's picrate, and authentic hexamine methopicrate melted at 195—196° alone or mixed. The melting point of dimethylhexamine dipicrate was reported from McGill and Bristol as 212°. Authentic specimens of the dipicrate from Bristol (m. p. 212° in Bristol) with the dipicrate from either Knudsen's picrate or authentic hexamine methopicrate gave mixed m. p. 195—200°, and all specimens of the dipicrate prepared in Manchester by the Bristol and McGill methods and a specimen of the dipicrate which had m. p. 212° in Bristol have similarly shown m. p. 195—196° in Manchester. The position is closely similar to that found with hexamine methopicrate itself. It is more disquieting that mixtures of authentic hexamine methopicrate and of authentic dimethylhexamine dipicrate also melt at 195—200°. However, the analytical results leave no doubt that the product from both Knudsen's picrate and hexamine methopicrate is indeed dimethylhexamine dipicrate, and the rather anomalous melting points act as a further caution against relying too much on these rather high decomposition points.

The final test was made by Professor F. J. Llewellyn who, in *X*-ray powder photographs of the dipicrate from Knudsen's picrate (m. p. 195—196°) and authentic dipicrate (m. p. 212° in Bristol, 195—196° in Manchester), found identical patterns (see Plate).

The results from these three lines of work thus confirm the threefold identity and structure (III of Part I) for the Knudsen base salts.

X-Ray powder diagrams for dimethylhexamine dipicrate (north and south quadrants) and the methyl dipicrate from Knudsen's base (east and west quadrants).



[*To face p.* 1091.

A Consideration of the Production of Tetra-alkylammonium Derivatives of Hexamine.—Apart from the normal direct alkylation process by alkyl halides and esters, the methylhexamine cation arises, somewhat unexpectedly, in at least two other reactions: (1) Knudsen's reaction, between formaldehyde and ammonium sulphate and (2) the action of hot solvents on hexamine dinitrate. In both, the methylating agent must be formaldehyde. *N*-Methylation by formaldehyde has long been recognised. Thus Plöchl (*Ber.*, 1888, **21**, 2117), Brochet and Cambrier (*Compt. rend.*, 1895, **120**, 449, 557; *Bull. Soc. chim.*, 1895, [iii], **13**, 392), Eschweiler (*Ber.*, 1905, **38**, 880), Köppen (*ibid.*, p. 882), and especially Werner (*J.*, 1917, **111**, 844) have demonstrated the formation of mono-, di-, and tri-methylamine from aqueous formaldehyde and ammonium chloride. It seems certain that *N*-methylation in biological syntheses is due to formaldehyde (Robinson, *ibid.*, p. 876), probably by the reactions:

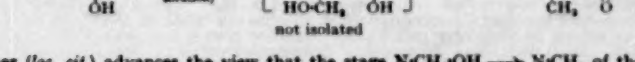
$$\text{>NH} \xrightarrow{CH_2O} \text{>N·CH}_2\text{·OH} \xrightarrow{2H} \text{>N·CH}_3$$

The first of these stages undoubtedly occurs (see, *e.g.*, Robinson, *J.*, 1936, 1079) and the overall process is well established.

The reducing agent needed for the second stage may be formaldehyde itself. Thus formaldehyde undergoes the Cannizzaro reaction in alkaline solution Lieben (*Monatsh.*, 1901, **22**, 289):

$$2CH_2O + H_2O \longrightarrow CH_3\text{·OH} + H\text{·CO}_2H$$

while from the formaldehyde–ammonium chloride methylation reaction (acid conditions) Werner (*loc cit.*) has isolated methyl formate. The formic acid produced can, itself, act as a reducing agent: $H\text{·CO}_2H \longrightarrow (2H) + CO_2$. In all these reactions carbon dioxide is evolved, especially at high temperatures (*ca.* 70°). If some other reducing system is present, *e.g.*, >CH·OH, it may be used. Thus Hess (*Ber.*, 1913, **46**, 4104) has shown that the following process occurs in the hygrine series:

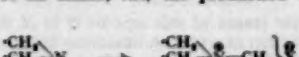


Werner (*loc. cit.*) advances the view that the stage $\text{N·CH}_2\text{·OH} \longrightarrow \text{N·CH}_3$ of the process goes by the steps $\text{NHR·CH}_2\text{·OH} \longrightarrow \text{NR:CH}_2 + H_2O \xrightarrow{CH_2O} \text{NHR·CH}_3 + H\text{·CO}_2H$.

In view of the extreme ease of hydrolysis of the aldimines (see, *e.g.*, Taylor and Baker in Sidgwick's "Organic Chemistry of Nitrogen," Oxford, 1947, p. 65) the existence of NR:CH_2 in appreciable amount in dilute acid solution is most unlikely. Moreover, Werner's view forces him to propose a most artificial mechanism to account for the production of trimethylamine.

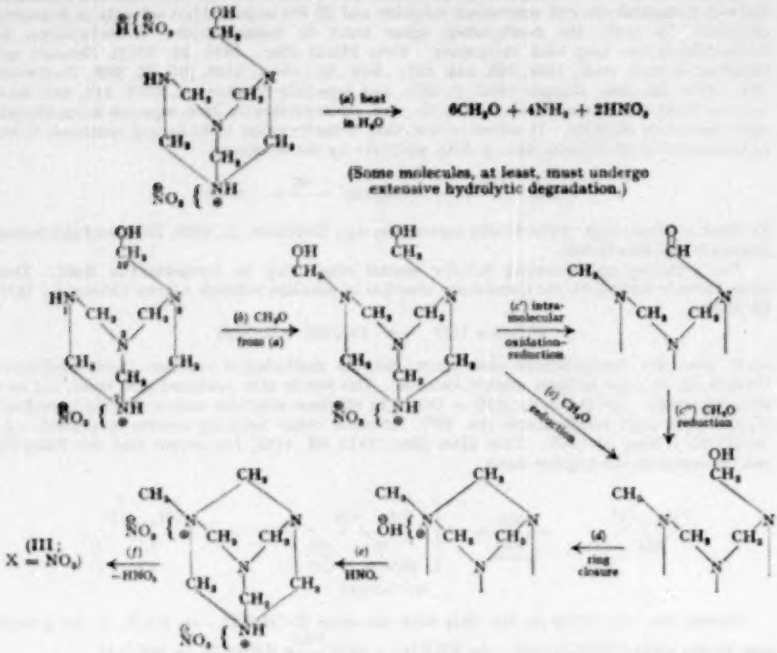
The less involved hypothesis of direct reduction of $\text{N·CH}_2\text{·OH}$ seems preferable. It may well be that, once the initial *N*-methylation has occurred, the N·CH_3 system is "stored" in the form of methylbishydroxymethylamine or 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane. Werner claims that the absence of "condensation products," including 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane, from the milder low-temperature reactions of formaldehyde with ammonium chloride is proved by the non-appearance of a precipitate on the addition of picric acid. This evidence is not conclusive since pre-formed 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane is not thus precipitated. It *is* possible, however, that the compound is not stable in acid solution.

Outside the hexamine field it does not appear that formaldehyde can effect the final stage in the complete methylation of an amine, *i.e.*, the production of the quaternary tetra-alkyl ammonium salt:



Indeed, it seems likely that so mild a reagent acting through so labile an intermediate as the $\text{N·CH}_2\text{·OH}$ system would be unable to achieve the drastic final stage in which the nitrogen atom is constrained permanently to the quadricovalent ammonium state, but would more readily replace hydrogen atoms attached to nitrogen in the tercovalent electrostatically-neutral state.

It is suggested, therefore, that the production of hexamine methonitrate from hexamine dinitrate proceeds through the " cage-opened " structure as follows:



This scheme is necessarily more clear-cut and formalised than the actual process is likely to be. With the exception of the reduction (*c*) and the ring closure (*d*) * all the steps involved are reversible. Each $>N\cdot CH_2\cdot OH$ system exhibits the tautomerism, $>N\cdot CH_2\cdot OH \rightleftharpoons >NH + CH_2O \rightleftharpoons >\overset{\oplus}{N}{:}CH_2\}OH^{\ominus}$ (cf. the tautomerism of cotarnine). It is not certain in what order the earlier steps occur. Thus the reduction of $N\cdot CH_2\cdot OH$ to $N\cdot CH_3$ may occur quite early at $N—CH_2\cdot OH$. Similarly the exchange of OH for NO_3, placed above at (*e*), may occur earlier by $>N\cdot CH_2\cdot OH \longrightarrow >N\cdot CH_2\cdot O\cdot NO_2$. It may well be that the critical reduction proceeds by processes (*c'*) and (*c''*) rather than by the direct process (*c*). The process (*c'*) is to be expected from the results of Hess (*loc. cit.*).

The fact that dimethylpentamethylenetetramine derivatives do not arise can be correlated with the probable properties of the methylhydroxymethylpentamethylenetetramine derivative produced after process (*c*) [or (*c'*) and (*c''*)]; this might well undergo irreversible ring closure * by process (*d*), in preference to further reduction to a dimethylpentamethylenetetramine derivative.

In connection with the later stages of this scheme it is of considerable interest that the *primary* crude product of the action of water on hexamine dinitrate is a water-soluble material giving a strongly acid solution and very similar to, indeed probably identical with, the hexamine nitrate methonitrate, m. p. 150°, prepared by workers in the University of Pennsylvania (private communication from Professor Marvin Carmack). The relative instability of this

* The ring closure (*d*) is likely to be irreversible because in the product $N_{(1)}$ is constrained to the quaternary tetra-alkylammonium state and N–C bonds are stronger than N–C bonds.

substance and its tendency to lose nitric acid, giving hexamine methonitrate, fits in with the difficulty with which the hexamine molecule retains a double positive ionic charge.

The possibility that hexamine methonitrate arises from hexamine dinitrate by process (*a*), followed by the methylation of some of the ammonia to methylamine and resynthesis of the hexamine cage from formaldehyde and base incorporating the methylamine, rather than by direct methylation of pre-formed hexamine, is not ruled out by the experimental observations; indeed the later stages of some such process must occur in our preparation of hexamine methohydroxide from formaldehyde, ammonia, and methylamine, Knudsen's alternative preparation of his base from hexamine and methylammonium nitrate, and in the production of the dimethylhexamine cage by the Bristol and McGill reactions.

Experimental.

(For additional analyses, see table, p. 1692).

3 : 7-*Dinitro*-1-*methylpentamethylenetetramine* 1-*Nitrate*.—Authentic hexamine methonitrate was treated with nitric acid under the conditions used in the University of Pennsylvania. Hexamine methonitrate (10 g.) was added gradually with stirring to nitric acid (50 ml. of 98%) at −10°. The stirring was continued for ½ hour, and the reaction mixture was then poured on crushed ice (300 g.). The mixture was kept for ½ hour, and the precipitate was then collected, washed with water, alcohol, and ether, and dried; it had m. p. 142° (9 g.).

3 : 7-*Dinitro*-1-*methylpentamethylenetetramine* 1-*Picrate*.—(*a*) The corresponding nitrate was suspended in water (in which it is only sparingly soluble), and saturated aqueous picric acid was added. The *picrate* separated as yellow-orange needles and was washed with water, alcohol, and ether, and dried. It had m. p. 141° (yield 80%) (Found: C, 30·9; H, 3·4; N, 27·4; CH_2, 2·6; *N*-CH_3, 5·2; picrate ion, 49·3. $C_{19}H_{15}O_{11}N_9$ requires C, 31·1; H, 3·3; N, 27·4; CH_2, 3·0; *N*-CH_3, 6·3; picrate ion, 49·3%).

(*b*) Authentic hexamine methopicrate (4 g.) was dissolved in nitric acid (40 ml. of 98%) at 0°. The mixture was kept at 0° for ½ hour and then poured gradually, with stirring, into ice–water (200 ml.). The product had m. p. 141° (3·4 g.).

(*c*) Knudsen's base picrate was treated with nitric acid as in (*b*) with identical results.

3-*Nitroso*-5-*nitro*-1-*methylpentamethylenetetramine* 1-*Picrate*.—(*a*) Authentic hexamine methopicrate (3 g.) was added with stirring at 0° during 4 minutes to nitric acid (25 ml. of 98%) containing dinitrogen tetroxide (9 g.). The reaction mixture was stirred at 0° for a further 2 minutes and then poured on crushed ice (200 g.). Golden-yellow crystals separated. After being washed with water, alcohol and ether, these had m. p. 129° (2·2 g.).

(*b*) A similar experiment with Knudsen's base picrate gave identical results.

1 : 5-*Dimethylhexamine* 1 : 5-*Dipicrate*.—(*a*) Following the University of Bristol procedure, 1 : 3 : 5-trimethyl-1 : 3 : 5-triaza*cyclo*hexane (0·33 mol.; prepared from methylamine and formaldehyde, following Henry, *Ber.*, 1893, **26**, *R*934) was added to paraformaldehyde (1 mol.) and ammonium nitrate (0·33 mol.), followed by nitric acid (6 mols. of 70%). The mixture was kept at 25° overnight. On the addition of methyl alcohol, 1 : 5-dimethylhexamine 1 : 5-dinitrate was precipitated. Purified by dissolution in nitric acid (70%) and re-precipitation with methyl alcohol, this had m. p. 193° (Dr. A. Carruthers reports m. p. 193°) (yield 30%). The dinitrate was dissolved in water and immediately treated with saturated aqueous picric acid. The precipitated dipicrate, after being washed with water, alcohol, and ether, and dried, had m. p. 195—196° (see, however, p. 1692) (yield, 80%).

(*b*) By a process analogous to the McGill University technique, authentic hexamine methopicrate (2 g.) and methylamine hydrochloride (1 g.) were heated at 50° in a mixture of acetic acid (25 ml.) and acetic anhydride (50 ml.) for 45 minutes. The solution was cooled and excess of saturated aqueous picric acid was added. The resulting orange crystalline precipitate, when washed with water, alcohol, and ether, and dried, had m. p. 195—196° (0·4 g.). A similar experiment with Knudsen's base picrate, gave an identical result.

A further experiment of this type was carried out using the crude mixture of Knudsen's base chloride and methylamine hydrochloride, together with acetic acid and acetic anhydride at 50°. The addition of picric acid precipitated the desired dipicrate, in low overall yield.

The authors acknowledge the assistance of Professor F. J. Llewellyn with the *X*-ray powder photography, helpful discussions with Dr. E. Roberts (E.R.D.E.), Dr. A. Carruthers and Dr. N. H. Woodbury (Bristol), and with Dr. F. B. Strauss (Oxford), and extensive private communications from Professors Marvin Carmack (University of Pennsylvania) and Carl Winkler (McGill University). The authors thank the Chief Scientist of the Ministry of Supply for permission to publish this paper.

University of Manchester.
Explosives Research and Development Establishment,
Ministry of Supply.

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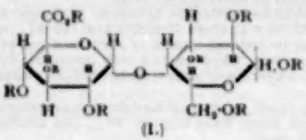
343. *Grapefruit and Lemon Gums. Part I. The Ratio of Sugars present in the Gums and the Structure of the Aldobionic Acid (4-D-Glucuronosido-D-galactose) isolated by Graded Hydrolysis of the Polysaccharides.*

By J. J. Connell, (Miss) Ruth M. Hainsworth, E. L. Hirst, and J. K. N. Jones.

The gums isolated from the grapefruit tree and the lemon tree are shown to be composed of residues of L-arabinose, D-galactose, and D-glucuronic acid (grapefruit gum: arabinose 16, galactose 53, glucuronic acid 31%; lemon gum: arabinose 22, galactose 55, glucuronic acid 22%). The reactions between these gums and the periodate ion have yielded information concerning structure. On hydrolysis the gums give an aldobionic acid, identified as 4-D-glucuronosido-D-galactose, since after methylation and hydrolysis it yields 2 : 3 : 4-trimethyl D-glucuronic acid and 2 : 3 : 6-trimethyl D-galactose. Other aldobionic acids may also be present.

Plant gums hitherto examined have been found to contain residues of D-galactose and a uronic acid. Most of them contain also L-arabinose, present in its furanose form, whilst some contain as well other sugar residues such as D-xylopyranose, L-rhamnopyranose, L-fucopyranose, and D-mannopyranose. In 1936 Anderson, Russell, and Seigle (*J. Biol. Chem.*, 1936, **113**, 683) described a sample of lemon gum which contained L-arabinose, D-galactose and D-glucuronic acid only. It appeared possible, therefore, that the structure of this gum might be relatively simple, in contrast with the complex nature of polysaccharides such as gum arabic, damson gum, and egg plum gum. It was decided, therefore, to investigate, in greater detail, the structure of lemon gum and of grapefruit gum. Through the kindness of Dr. Misener of Toronto and of Professor E. T. Bartholomew of the Agricultural Experimental Station, The University of California, we were able to obtain samples of known origin and previous history. The gums were supplied to us in the form of pale yellow, brittle solids possessing a characteristic aromatic smell. By dissolution in water followed by precipitation with acidified alcohol they were obtained as white, ash-free, water-soluble, acidic powders. The samples of grapefruit gum were characterised by their optical rotation ($[\alpha]_D$ *ca.* +56°) and equivalent weight (*ca.* 590), whilst the lemon gum had a lower rotation ($[\alpha]_D$ *ca.* +20°) and a higher equivalent weight (*ca.* 790). These values were characteristic for the gums and independent of the place in which the tree was growing. It would appear from these and other results (*cf.* Hirst, *J.*, 1942, 70) that the gum produced by a fruit tree is specific to the type of tree.

The pentose residues in both grapefruit and lemon gum are present in the furanose form since they undergo hydrolysis under very mild acid conditions. Further hydrolysis of the polysaccharides with dilute acid (0·1N.) results in the formation of D-galactose and an aldobionic acid (I; R = H), which is converted into D-galactose and D-glucuronic acid when heated with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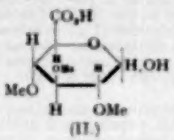
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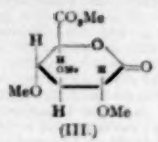
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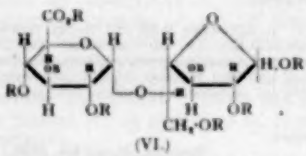
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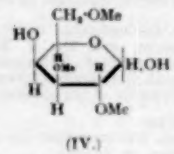
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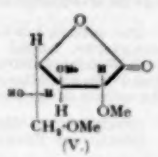
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more concentrated acid. Methylation of the aldobionic acid gives an octamethyl derivative (I; R = Me) which on hydrolysis yields (*a*) 2 : 3 : 4-trimethyl D-glucuronic acid (II), identified after oxidation and esterification as the methyl ester of 2 : 3 : 4-trimethyl D-saccharopyranolactone (III), and (*b*) ? 2 : 3 : 6-trimethyl D-galactose (IV), identified after oxidation as the crystalline 2 : 3 : 6-trimethyl D-galactofuranolactone (V). The aldobionic acid is, therefore, either (VI) in which a D-galactofuranose residue is linked through $C_{(1)}$, or (I; R = H) in which a D-galactopyranose residue is linked through $C_{(4)}$. The rotation of the aldobionic acid favours

the pyranose structure which is moreover in accord with the general occurrence of galactopyranose residues in plant gums. The yield of this aldobionic acid was poor and the presence of other aldobionic acid residues in the gum cannot yet be definitely excluded.

Information on the structure of grapefruit gum and lemon gum was obtained from a study of their reactions with periodate. The yield of formic acid obtained by oxidation of a non-reducing polysaccharide with periodate is a measure of the amount of pyranose end group and of hexopyranose residues united through $C_{(1)}$ and $C_{(2)}$ only. By periodate oxidation, grapefruit gum gives 0·5 mole of formic acid per equivalent, whilst lemon gum gives 1 mole per equivalent. Thus grapefruit gum contains a repeating unit of 1180 (equivalent weight, 590) or multiples of 1180, whilst that of lemon gum is 790 or a multiple of this number. The uptake of periodate during the reaction shows that several sugar residues are oxidised. For instance, with grapefruit gum the consumption of periodate is 4 moles per repeating unit of 1180. Now the formation of 1 mole of formic acid requires two moles of periodate and therefore two sugar residues other than the one which yields formic acid are oxidised during the reaction. Lemon gum on the other hand consumes 3·2 moles of periodate per molecule of 790, and in this case one sugar residue other than the one giving formic acid must be oxidised. The results now recorded show that in both lemon gum and grapefruit gum, L-arabinose residues occur which are not oxidised by the periodate ion and must, therefore, be substituted on $C_{(3)}$ or $C_{(4)}$. Grapefruit gum would appear, therefore, to be built on lines as complicated as those of other plant gums.

Both lemon gum and grapefruit gum contain a considerable percentage of D-galactose residues which are not attacked by the periodate ion and therefore possess no contiguous hydroxyl groups. It follows that 1 : 3-linked galactose residues such as are encountered it damson, cherry, and egg plum gum, and in gum arabic, occur also in grapefruit and lemon gum.

Experimental.

The samples of grapefruit and lemon gum were obtained from Dr. T. Misener and the Seminola Co., Florida, and from Professor E. T. Bartholomew of The Agricultural Experimental Station, University of California. They were soluble in water giving viscous light brown solutions, from which they were precipitated by the addition of alcohol or acetone. The purified ash-free materials were prepared by precipitation of the polysaccharide from a solution acidified with hydrochloric acid by the addition of alcohol or glacial acetic acid. The precipitates were washed by decantation with alcohol, filtered off, washed with alcohol, then with ether, and finally dried at 40° under reduced pressure. The gums were isolated as white powders, soluble in water and aqueous sodium hydroxide with the formation of colourless non-reducing solutions. Addition of copper salts, calcium salts, or silver salts to solutions of the neutral sodium salt of grapefruit precipitated the insoluble blue copper, or insoluble white calcium or silver salt. The acidic, ash-free gum could be regenerated by treatment of the salts with alcohol containing hydrochloric acid. Lemon gum also gave an insoluble copper salt.

Grapefruit Gum.—Samples of this gum had been obtained from trees growing in California and from one tree growing in Florida. All the specimens had similar properties and this applied also to samples which had exuded from a *Phytophthora*-infected tree. The equivalent weights, determined by direct titration with 0·1N-sodium hydroxide (phenolphthalein) varied from 582 to 596. $[\alpha]_D$, in water, for the various samples lay between +54° and +59°. These values are so close to one another that it is considered that the samples are essentially identical in their physical properties (Found : furfuraldehyde after boiling of the gum with 12% hydrochloric acid, 16·6; uronic anhydride, 31·3; OMe, 5·2%). The polysaccharide on oxidation with nitric acid (*d* 1·2) gave mucic acid in yield equivalent to the presence of at least 40% of galactan. Methyl pentose was not present, since no methylfurfuraldehyde was obtained on distillation with 12% hydrochloric acid, and the sugars obtained on hydrolysis of the gum gave no acetaldehyde on oxidation with periodic acid (method of Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456).

Examination of the mixture of neutral sugars on the paper chromatogram showed the presence of galactose and arabinose only (Found : furfuraldehyde after boiling of the sugars with 12% hydrochloric acid, 16·6; uronic acid anhydride, 31·3%). This percentage of uronic anhydride would yield 6·9% of furfuraldehyde and therefore 16·6 − 6·9 = 9·7% arise from arabinose. This corresponds to the presence of *ca.* 16% of arabinose (calc. as $C_5H_{10}O_5$) in the molecule. On the basis of the observed analytical figures for arabinose and uronic acid residues, the amount of galactose residues in the gum is (by difference) 52·7%.

Periodate Oxidation of Grapefruit Gum.—(*a*) The potassium salt of the gum (45·4 mg.) in water (8 c.c.) was oxidised with an excess of sodium periodate solution (2 c.c.; 0·25M.) during 7 days. Excess of sodium periodate was then destroyed by the addition of ethylene glycol, and the formic acid was determined by titration [Found : 1·67 mg., equivalent to the formation of 1 mole of formic acid per two equivalents (1012 g.) of gum]. In a second experiment the amount of periodate reduced to iodate in 7 days by the potassium salt of the gum (46·8 mg.) was determined (Found : 1·71 c.c. of M/10-sodium periodate, equivalent to 2 moles of sodium periodate reduced per 549 g. of the ash-free gum).

(*b*) The potassium salt of the gum (0·122 g.) was oxidised with sodium periodate solution (5 c.c.; 0·25M.) for 3 days. (Preliminary experiments had shown that oxidation was complete in this time.) Ethylene glycol was added to destroy excess of sodium periodate and the solution was then dialysed until free from iodate ions. The solution was evaporated to dryness at 50° under reduced pressure and the residual oxidised polysaccharide dried to constant weight (Found : sulphated ash, 7·8%).

The oxidised polysaccharide was hydrolysed at 100° with N-sulphuric acid for 3 hours. The cooled solution was neutralised with barium carbonate and filtered, and the filtrate evaporated to a syrup. Separation on the paper chromatogram showed the presence of arabinose and galactose.

Graded Hydrolysis of Grapefruit Gum.—Purified ash-free grapefruit gum (16 g.) was heated with water (550 c.c.) at 90°, the acidity of the solution being sufficient to bring about slow hydrolysis of the gum. The reaction was followed by polarimetric and iodometric observations: $[\alpha]_D^{20}$ +63° (3 hours, initial value not observable); +56° (7·5 hours); +60° (12 hours); +61° (19 hours); +63° (31 hours); +66° (39 hours); +66° (43 hours); +68° (53 hours). A much slower hydrolysis proceeded beyond this stage. The increase in iodine titre was followed by titration of 2-c.c. portions of the solution with 0·1N-iodine by Baker and Hulton's method (*Biochem. J.*, 1920, **14**, 754): value (in c.c. of 0·1N-iodine, calc. for 1 g. of grapefruit gum), 1·4 (initial); 5·5 (1 hour); 11·0 (3·2 hours); 16·5(7·5 hours); 22·0 (12 hours); 28·2 (19 hours); 33·0 (31 hours); 37·8 (39 hours); 38·5 (43 hours); 40·0 (53 hours). The cooled solution was concentrated, at 40°/12 mm., to 200 c.c. and poured into alcohol; it then gave an alcohol-insoluble polysaccharide (*A*) (5·1 g.) which was washed with alcohol and dried.

The filtrate from (*A*) still contained some acidic material; it was, therefore, evaporated to a syrup at 40°/12 mm., diluted with water, neutralised with barium carbonate, and filtered, and the filtrate poured into alcohol. The precipitated material (10·5 g.) (*B*) was apparently the barium salt of polysaccharide (*A*) which had escaped precipitation. It was filtered off, washed, and dried. The filtrate from (*B*) was evaporated to a syrup (3·3 g.) which was dissolved in water (50 c.c.). An iodine titration at this stage indicated the presence of reducing sugar (2·8 g., calc. as pentose; 3·3 g., calc. as hexose). A furfuraldehyde determination showed the presence of 1·2 g. of pentose, and this was shown to be L-arabinose since quantitative determination with diphenylhydrazine indicated the presence of 1·2 g. of L-arabinose. This value corresponds to the presence in the polysaccharide of some 7% of arabinose, calc. as $C_5H_8O_5$. Oxidation of a portion of the syrup with nitric acid (*d* 1·2) showed the presence of approximately 1·8 g. of galactose. A mixture of 1·2 g. of L-arabinose and 1·8 g. of D-galactose would have $[\alpha]_D^{20}$ +90° and would reduce 360 c.c. of N/10-iodine (Found: $[\alpha]_D^{20}$ +87°; 368 c.c. of N/10-iodine). On the paper chromatogram no sugars other than arabinose and galactose could be detected.

Examination of barium salt (B). This material was isolated as a white powder, easily soluble in water to yield a pale yellow solution, and had $[\alpha]_D^{20}$ +73° (*c*, 2·08 in water). The salt reduced Fehling's solution on boiling and reduced alkaline iodine solution (1 g. reduced 27·5 c.c. of 0·1N-iodine). On heating with 12% hydrochloric acid, carbon dioxide equivalent to the presence of 36% of uronic anhydride, and furfuraldehyde (14·4%) were evolved. The salt contained barium (13·4%) and methoxyl (9·3%; a partly etherified sugar acid may have been present).

The barium salt (6 g.) was dissolved in N-sulphuric acid (100 c.c.) and heated at 95° for 4 hours, the following changes being observed: (*a*) $[\alpha]_D^{20}$ +74° (initial value); +84° (30 minutes); +88° (70 minutes); +89° (2·2 hours); +86° (4 hours); (*b*) iodine titre, in c.c. of 0·1N-iodine per gram of barium salt, 25 (initial value); 36 (30 minutes); 42 (70 minutes); 50 (2·6 hours); 52 (4 hours). The cooled solution was neutralised with barium carbonate and filtered, and the filtrate concentrated to a solid (OMe, 3·1%), which was extracted with alcohol. On concentration the extracts (3·5 g.) gave D-galactose, m. p. 164°, $[\alpha]_D^{20}$ +77°, and a syrup consisting of D-galactose, admixed with a small quantity (*ca.* 0·1 g.) of L-arabinose. The barium salt appeared to be identical with the barium salt isolated after hydrolysis of polysaccharide (*A*) (see below).

Polysaccharide (A). This material was a pale buff-coloured powder, easily soluble in water to give a solution which was acidic, reduced Fehling's solution slightly on boiling, and had $[\alpha]_D^{20}$ +25° (in water) [Found: ash, 0·3; OMe, 2·7%; furfuraldehyde (after boiling with 12% hydrochloric acid), 8·1; uronic anhydride (from the weight of carbon dioxide evolved in boiling with 12% hydrochloric acid), 37·7%; equiv. (by titration with 0·1N-sodium hydroxide), 530]. D-Galactose was present since mucic acid was formed on oxidation of a portion of the polysaccharide with nitric acid (*d* 1·2). The polysaccharide (4 g.) was hydrolysed with N-sulphuric acid (50 c.c.) for 5 hours ($[\alpha]_D$ not observable owing to darkening of the solution). The cooled solution was neutralised by titration with 0·33N-barium hydroxide and filtered, and the filtrate concentrated in a vacuum. The residue was exhaustively extracted with methyl alcohol and the extracts were concentrated under reduced pressure to a syrup (1·8 g.), $[\alpha]_D^{20}$ +78°, which crystallised. The crystalline sugar (1·6 g.), separated by trituration with alcohol, had m. p. and mixed m. p. with D-galactose, 165°. The residual barium salt showed $[\alpha]_D^{20}$ +78° in water (Found: Ba, 17·8. Calc. for the barium salt of an aldobionic acid: Ba, 16·0%). This barium salt was very resistant to hydrolysis but was hydrolysed, with much decomposition, by 2N-sulphuric acid. Owing to darkening of the solution it was not possible to observe the change in optical rotation. The sugar, isolated from the hydrolysate in the usual manner, was identified as D-galactose, m. p. and mixed m. p. 164°, $[\alpha]_D^{20}$ +81° (in water, equilibrium value).

It was possible to isolate the barium salt of the aldobionic acid in good yield by the following simplified procedure. The gum (7·2 g.; ash-free) was dissolved in 0·1N-sulphuric acid (50 c.c.), and the solution heated on the boiling water-bath for 20 hours. The cooled solution was neutralised with barium carbonate and filtered and the filtrate concentrated under reduced pressure to a syrup which was poured into alcohol. The insoluble barium salt of the aldobionic acid was collected, washed with alcohol, and dried (yield, 4 g.). The alcoholic filtrate was concentrated and a portion examined on a paper chromatogram which showed the presence of galactose together with a trace of arabinose.

Methylation of the aldobionic acid. The barium salt (4 g.) was dissolved in water (10 c.c.), and methyl sulphate (25 c.c.) was added. Sodium hydroxide (50 c.c.; 40%) was added drop-wise during 12 hours, the solution then not reducing Fehling's solution. The reaction mixture was concentrated to a small volume and re-methylated by dissolving the residue in sodium hydroxide (100 c.c.; 40%) and adding methyl sulphate (70 c.c.) drop-wise. After 24 hours' stirring the solution was concentrated on the steam-bath, cooled, and acidified with sulphuric acid, and the methylated aldobionic acid extracted with chloroform (six times). The extracts were dried and filtered and the solvents removed under reduced pressure. The residual syrup was dissolved in methyl iodide and methylated by the portion-wise addition of silver oxide. The product (3·1 g.; n_D^{20} 1·4678) (Found: OMe, 51·8%) was isolated, in the usual manner,

as a pale yellow syrup. It was purified by fractional distillation. The low-boiling fraction (0·2 g.; n_D^{20} 1·4555) (Found: OMe, 56·5%) was not further examined. The main fraction (2·1 g.), b. p. 160—220°/1 mm., had n_D^{20} 1·4695 and $[\alpha]_D^{20}$ +81° (*c*, 0·7 in methyl alcohol) (Found: OMe, 51·7%).

The methylated aldobionic acid (0·81 g.) was hydrolysed by boiling it with N-sulphuric acid (20 c.c.) for 16 hours ($[\alpha]_D$ not observable). The cooled solution was neutralised with aqueous sodium hydroxide, and the methylated sugar was isolated by exhaustive continuous extraction with chloroform. The product (0·36 g.), $[\alpha]_D^{20}$ +90° (*c*, 0·4 in water), was identified as 2 : 3 : 6-trimethyl D-galactose (Found: OMe, 41·1. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). On oxidation with bromine water in the usual manner the sugar gave 2 : 3 : 6-trimethyl D-galactofuranolactone, b. p. 140°/1 mm., n_D^{20} 1·4565 (super-fused solid), m. p. and mixed m. p. 98° after recrystallisation from ether, $[\alpha]_D^{20}$ being −44° (initial value), −40° (21 hours), −37° (4 days) (Found: Equiv., 211; C, 49·0; H, 7·4; OMe, 42·0%. Calc. for $C_9H_{16}O_6$: equiv., 220; C, 49·1; H, 7·3; OMe, 42·3%).

After removal of the sugars from the hydrolysate (above) the solution was acidified with sulphuric acid and the uronic acid residue (0·45 g.) isolated by further continuous extraction. The product was oxidised with bromine water, and the resultant saccharic acid derivative isolated in the usual manner. This material was boiled with methanolic hydrogen chloride, and the resultant ester was isolated. On distillation the methyl ester of 2 : 3 : 4-trimethyl D-saccharolactone was obtained, having b. p. 140°/0·1 mm., n_D^{20} 1·4570 (Found: OMe, 49·8. Calc. for $C_{10}H_{18}O_7$: OMe, 50·0%). This material crystallised when kept. Recrystallised from ether, it had m. p. 109°, not depressed on admixture with an authentic specimen but depressed to 80—85° on admixture with dimethyl 2 : 3 : 4-trimethyl D-mucate.

Lemon Gum.—Several samples of lemon gum were examined, one from a *Phytophthora*-infected Eureka lemon tree growing on sour orange root-stock and others from lemon trees infected with unknown organisms. In all cases examined the ash-free gum possessed an equivalent weight of 770—800 and $[\alpha]_D$ (as sodium salt in water) between +19·5° to +21·2° (cf. Anderson, Russel, and Seigle, *J. Biol. Chem.*, 1936, **113**, 683, who give a value of +20·7°) (Found: OMe, 4·0; furfuraldehyde, after boiling with 12% hydrochloric acid, 16·6; uronic acid anhydride, from the yield of carbon dioxide after boiling with 12% hydrochloric acid, 22·4%). Methyl pentose was absent.

The amount of uronic anhydride found would give rise to 5·0% of furfuraldehyde and, therefore, 16·6 − 5·0 = 11·6% arises from arabinose. This corresponds to the presence of *ca.* 22% of arabinose (calc. as $C_5H_{10}O_5$), in the molecule. The difference, *ca.* 55%, is, therefore, galactose (calc. as $C_6H_{12}O_6$).

Examination, on the Paper Chromatogram, of the Sugars produced by Hydrolysis of Lemon Gum.—The ash-free gum (13·04 mg.) was hydrolysed with N-sulphuric acid (0·4 c.c.) containing rhamnose (4·38 mg.), on the steam-bath for 3 hours. The cooled solution was neutralised with barium carbonate, and the sugars present in a portion of the supernatant liquid were separated on the paper chromatogram and determined by the Somogyi copper reagent (Found: 0·222 mg. of rhamnose; 0·0584 mg. of arabinose; 0·104 mg. of galactose). These values correspond to the removal by hydrolysis of 21·2% of arabinose residues and of 38·6% of galactose residues (Calc. as $C_5H_9O_4$ and $C_6H_{11}O_5$ respectively), leaving a resistant core (40·2%) of sugar residues [Calc. for one aldobionic acid unit (consisting of a D-galactose and a D-glucuronic acid residue) per equivalent of polysaccharide, 42·8%].

Oxidation of Lemon Gum with Potassium Periodate.—(*a*) The neutral potassium salt of the polysaccharide (42·8 mg.) in water (10 c.c.) containing potassium chloride (0·3 g.) was oxidised with sodium periodate (0·2 c.c.; 0·25M.) for 150 hours. Ethylene glycol was then added and the formic acid determined by titration [Found: 2·48 mg., equivalent to the formation of approximately 0·98 mole of formic acid per equivalent (775) of the gum].

(*b*) The potassium salt of the gum (42 mg.) was oxidised with sodium periodate (0·2 c.c.; 0·25M.) made up to 10 c.c. with water containing potassium chloride (0·3 g.), for 150 hours. At the end of this time the consumption of periodate was determined (Found: 1·66 c.c. of M/10-solution, equivalent to a consumption of 3·2 moles of periodate per equivalent of ash-free polysaccharide of equiv. wt. 775).

Examination of the Material obtained by the Oxidation of Lemon Gum with Potassium Periodate.—The gum (0·25 g.) was oxidised with potassium periodate (0·75 g.) for 150 hours as described above. The excess of periodate was then removed by addition of ethylene glycol and the solution was dialysed against running water until free from inorganic ions. The dialysed solution was evaporated to dryness and the solid was dried to constant weight (75 mg.). The oxidised polysaccharide was hydrolysed with N-sulphuric acid on the steam-bath for 4 hours. The cooled solution was neutralised with barium carbonate, and the sugars were separated on the paper chromatogram. Arabinose and galactose were the only sugars detected.

Hydrolysis of Lemon Gum.—Lemon gum (5 g.) was dissolved in N-sulphuric acid (11 c.c.) and water (39 c.c.), and the solution was heated on the steam-bath, the following changes being observed: $[\alpha]_D^{20}$ +21·8° (initial value); +34° (½ hour); +42° (1½ hours); +49° (2½ hours); +56° (4 hours); +60° (5 hours); +64° (6 hours); +74° (9 hours); +78° (11 hours); +89° (20 hours). A sugar determination at this stage indicated the presence of *ca.* 3·4 g. of reducing sugar, calculated as hexose. At this stage, a small sample of the solution was examined on the paper chromatogram: galactose and arabinose were the only sugars present.

Isolation of octamethyl 4-D-glucuronosido-D-galactose. The mixture of reducing sugars was stirred with methyl sulphate (25 c.c.), and sodium hydroxide (25 c.c.; 30%) added drop-wise with vigorous stirring at 25° until the solution was non-reducing to Fehling's reagents. At this stage an excess of sodium hydroxide (50 c.c.; 30%) was added and the methylation continued by the portion-wise addition of methyl sulphate (40 c.c.). After completion of the addition the solution was heated to 60°, cooled, and extracted exhaustively with chloroform to remove methylated sugars. The solution was then made acid with dilute sulphuric acid and the extraction continued. Concentration of the acidic extracts left a syrup (2·35 g.) which was methylated with silver oxide and methyl iodide (twice) and distilled fractionally giving fractions I (0·32 g.), b. p. 160°/1 mm., n_D^{20} 1·4518 (Found: OMe, 58·2%), and II (1·1 g.), b. p. 190°/0·1 mm., n_D^{20} 1·4685 (Found: OMe, 51·1%).

Fraction II (0·94 g.) was hydrolysed by boiling a solution of it in N-sulphuric acid (20 c.c.). The optical rotation was not observable owing to the opalescence of the solution. After 20 hours the solution

was neutralised with barium carbonate and extracted continuously with chloroform, yielding an extract containing 2 : 3 : 6-trimethyl D-galactose and leaving an aqueous solution containing the barium salt of 2 : 3 : 4-trimethyl D-glucuronic acid. The 2 : 3 : 6-trimethyl D-galactose (0·3 g.) had n_D^{20} 1·4710, $[\alpha]_D^{20}$ +78° in water (Found: OMe, 40·6. Calc. for $C_9H_{18}O_6$: OMe, 41·8%). On oxidation with bromine water it yielded crystalline 2 : 3 : 6-trimethyl D-galactonolactone, m. p. 99° (after recrystallisation from ether), not depressed on admixture with an authentic specimen. The aqueous solution of barium 2 : 3 : 4-trimethyl D-glucuronate was acidified with sulphuric acid, and the 2 : 3 : 4-trimethyl D-glucuronic acid (n_D^{20} 1·4700, $[\alpha]_D^{20}$ +50°, in water) isolated by continuous extraction with chloroform. The syrupy acid (0·34 g.) was identified after oxidation with bromine water, followed by esterification, as the methyl ester of 2 : 3 : 4-trimethyl D-saccharopyranolactone, m. p. and mixed m. p. 110°.

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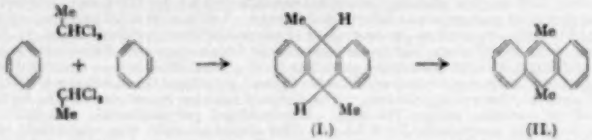
344. *Substituted Anthracene Derivatives. Part I.* cis- *and* trans-9 : 10-*Dimethyl*-9 : 10-*dihydroanthracene.*

By G. M. BADGER, (MISS) M. L. JONES, and R. S. PEARCE.

9 : 10-Dimethyl-9 : 10-dihydroanthracene (II) has been shown to exist in *cis*- and *trans*-forms.

AT least five erroneous descriptions of 9 : 10-dimethyl-9 : 10-dihydroanthracene (I) have appeared in the literature. For example, Angelbis and Anschütz (*Ber.*, 1884, **17**, 165) claimed to have obtained the hydrocarbon by interaction of ethylidene chloride and benzene in the presence of aluminium chloride. Somewhat similar preparations have been described by Anschütz (*Annalen*, 1886, **235**, 299), by Böeseken and Bastet (*Rec. Trav. chim.*, 1913, **32**, 184), by Cook and Chambers (*J. Amer. Chem. Soc.*, 1921, **43**, 334), and by Davidson and Lowy (*J. Amer. Chem. Soc.*, 1929, **51**, 2978). However, in a paper describing the preparation of 9 : 10-dimethylanthracene (II), Barnett and Matthews (*Ber.*, 1926, **59**, 1429; cf. Friedel and Crafts, *Bull. Soc. chim.*, 1884, **41**, 322; Anschütz and Romig, *Ber.*, 1885, **18**, 662) pointed out that the compound isolated by Anschütz and others could not be the dihydride as its properties (the relatively high melting point of 181°, the yellow colour, and the formation of a picrate) are those associated with a completely aromatic structure. They described Anschütz's hydrocarbon as 9 : 10-dimethylanthracene (II) and attributed its formation to the dehydrogenating action of aluminium chloride on the dihydride (I) initially formed.



(I.) (II.)

Authentic 9 : 10-dimethyl-9 : 10-dihydroanthracene (I) was first prepared by Badger, Goulden, and Warren (*J.*, 1941, 18) by the action of methyl iodide on the 9 : 10-disodio-addition product with anthracene. This compound, unlike that of Anschütz, had m. p. 101—102° and was readily dehydrogenated with sulphur. In Egloff's compilation ("Physical Constants of Hydrocarbons," Vol. 4, 1947), this work has been overlooked, Anschütz's hydrocarbon still being listed as 9 : 10-dimethyl-9 : 10-dihydroanthracene.

The work of Badger, Goulden, and Warren also appears to have been overlooked by Sisido and Isida (*J. Amer. Chem. Soc.*, 1948, **70**, 1289) who recently prepared a new 9 : 10-dimethyl-9 : 10-dihydroanthracene, m. p. 130°, by reduction of 9 : 10-dimethylanthracene with sodium and alcohol. This was very readily dehydrogenated to (II), even by treatment with aluminium chloride at room temperature. It seemed likely that the two dihydrides are *cis-trans*-isomers and, in order to clarify the position, the preparation of 9 : 10-dimethyl-9 : 10-dihydroanthracene has been re-investigated.

First, the preparation of the lower-melting dihydride by the above method was confirmed. This product was colourless, did not fluoresce in ultra-violet light, and did not form a picrate. Its dehydrogenation with sulphur to 9 : 10-dimethylanthracene was also confirmed, but it was

not dehydrogenated with aluminium chloride at room temperature. There seems no reason to doubt that this product is 9 : 10-dimethyl-9 : 10-dihydroanthracene, and its ultra-violet absorption spectrum (see Fig. 1) is consistent with this conclusion. Sisido and Isida's preparation of the higher-melting dihydride and the behaviour with aluminium chloride have also been confirmed. In our hands, however, this method gave a mixture from which *both* dihydrides were isolated. The higher-melting dihydride was also colourless, non-fluorescent, and did not form a picrate. The ultra-violet absorption spectrum (Fig. 2) of this dihydride is also consistent with its formulation as 9 : 10-dimethyl-9 : 10-dihydroanthracene.

There can be little doubt that the two dimethyl dihydrides discussed in this paper are *cis-trans*-isomers. The lower-melting form is provisionally regarded as the *cis*-compound. Incidentally, its less ready dehydrogenation indicates that the preparation of 9 : 10-dimethylanthracene by the methods of Anschütz and others proceeds *via* the higher-melting (*trans*)-dihydride.

FIG. 1.
Ultra-violet absorption in alcohol.

FIG. 2.
Ultra-violet absorption in alcohol.

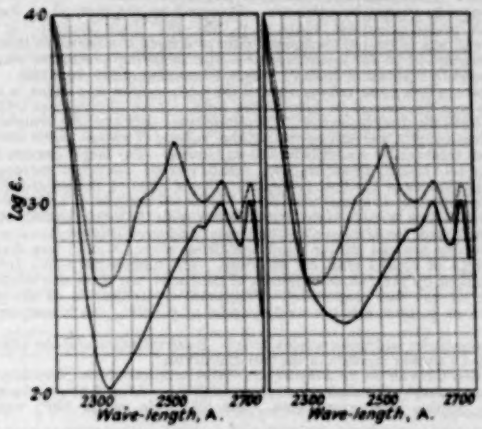


FIG. 1. – – – – – 9 : 10-*Dihydroanthracene*. *Max. at* 2520 (3·33), 2640 (3·10), 2710 A. (3·09).
———— cis(?)-9 : 10-*Dimethyl*-9 : 10-*dihydroanthracene*, *m. p.* 101—102°. *Maxima at* 2580 (2·85), 2640 (2·99), 2710 A. (3·01).

FIG. 2. – – – – – 9 : 10-*Dihydroanthracene*.
———— trans(?)-9 : 10-*Dimethyl*-9 : 10-*dihydroanthracene*, *m. p.* 130°. *Maxima at* 2580 (2·87), 2640 (3·01), 2710 A. (3·02).

A few *cis-trans*-isomers of this type have been reported previously. For example, Barnett, Cook, and Matthews (*Rec. Trav. chim.*, 1925, **44**, 728) described the isomeric 1 : 5-dichloro-9 : 10-dihydroxy-9 : 10-dihydroanthracenes, and dipole moment measurements confirmed the configurations assigned to them (Bergmann and Weizmann, *J. Amer. Chem. Soc.*, 1938, **60**, 1801).

If the configurations of the dimethyl dihydrides are correctly assigned, addition of sodium to anthracene is a pure *cis*-reaction, as is the addition of chlorine to 1 : 5-dichloro- and 9 : 10-diphenyl-anthracene. In the case of 1 : 8-dichloroanthracene, however, addition of chlorine is a *trans*-reaction, for the dipole moment of the dichloride is smaller than that of the parent compound (Bergmann and Weizmann, *loc. cit.*).

The disodio- and dilithio-derivatives of anthracene hydrocarbons are usually very different in colour, and Bachmann and Pence (*J. Amer. Chem. Soc.*, 1937, **59**, 2339) made the interesting hypothesis that this might be associated with *cis*-addition in one case, and *trans*- in the other. We therefore investigated the reduction of 9 : 10-dimethylanthracene by first forming the 9 : 10-disodio-(or lithio-)addition product, at room temperature, followed by treatment with methanol (cf. Bachmann and Pence, *loc. cit.*). In both cases, however, a mixture of the two dihydrides was formed, and in this instance, therefore, the hypothesis is incorrect. Treatment

with sodium ethoxide sometimes brings about stereochemical inversion (*e.g.*, at centres adjacent to an enolisable group; cf. Linstead and Doering, *J. Amer. Chem. Soc.*, 1942, **64**, 1991), but it does not do so in the present case, for the lower-melting dihydride was recovered unchanged after 2 hours' boiling with a concentrated solution of sodium ethoxide.

The ultra-violet absorption curves of the two dimethyl dihydrides, compared with that of 9 : 10-dihydroanthracene, are given in the accompanying Figures. The absorption curves of the isomers are almost identical, except that the lower-melting isomer has an absorption minimum of log ϵ_m 2·02 at 2340 A., while the corresponding minimum of the higher-melting isomer is 2·35 at 2400 A. The minimum in the curve for 9 : 10-dihydroanthracene is log ϵ_m 2·55 at 2320 A.

Experimental.

9 : 10-*Dimethylanthracene*.—Several useful methods for the preparation of this compound have already appeared (*e.g.*, Bachmann and Chemerda, *J. Org. Chem.*, 1939, **4**, 583; Badger, Goulden, and Warren, *loc. cit.*). The following method has also been found useful.

9 : 10-Bischloromethylanthracene (2 g.; Badger and Cook, *J.*, 1939, 802) in dioxan (350 c.c.) was hydrogenated over 30% palladised asbestos (0·25 g.). Removal of solvent and crystallisation from alcohol gave yellow needles of 9 : 10-dimethylanthracene, m. p. 180°.

cis(?)-9 : 10-*Dimethyl*-9 : 10-*dihydroanthracene*.—Prepared by the method of Badger, Goulden, and Warren (*loc. cit.*), this formed colourless blades, m. p. 101—102° (from alcohol). It was not fluorescent in ultra-violet light, and was recovered unchanged after prolonged irradiation in thin layers.

trans(?)-9 : 10-*Dimethyl*-9 : 10-*dihydroanthracene*.—The following procedure was more satisfactory than that recommended by Sisido and Isida (*J. Amer. Chem. Soc.*, 1948, **70**, 1289). To a suspension of 9 : 10-dimethylanthracene (0·7 g.) in boiling alcohol (50 c.c.), sodium was added in small portions until the solution became non-fluorescent in ultra-violet light. More alcohol was added, if required, to dissolve the sodium, until the disappearance of the fluorescence indicated the completion of the reaction. The resulting colourless solution was diluted with a large volume of water. After some time, the precipitate was collected and fractionally recrystallised from alcohol. The larger portion (0·4 g.) consisted of *trans(?)*-9 : 10-dimethyl-9 : 10-dihydroanthracene, which formed colourless rectangular plates, m. p. 130—131°. From the liquors of the first recrystallisation a little of the lower-melting dihydride was isolated; after recrystallisation, it formed colourless blades (50 mg.), m. p. and mixed m. p. 101°. The relative proportions of the two isomers varied considerably with the experimental conditions.

Reduction of **9 : 10-*Dimethylanthracene*** via *Alkali-metal Addition Compounds*.—A solution of dimethylanthracene (0·5 g.) in dry benzene (50 c.c.) and anhydrous ether (50 c.c.) was shaken with powdered sodium (1 g.) and chips of broken glass for 36 hours. The intense deep-blue colour of the disodio-derivative was discharged by the gradual addition of methanol, the glass and unchanged sodium were filtered off, and the solvent was evaporated. Fractional crystallisation of the product gave small amounts of the *trans*-, m. p. 130°, and the *cis*-dihydride, m. p. 101°. Both compounds were identified by mixed m. p.

Lithium gave a deep-violet addition complex with 9 : 10-dimethylanthracene which, after interaction with methanol, yielded a similar mixture of the two dihydrides.

Action of Aluminium Chloride on the Dihydrides.—(*a*) A solution of the dihydride, m. p. 101° (0·5 g.), in benzene (5 c.c.) was treated with aluminium chloride (2 g.). After 2 hours, the mixture was poured into water, and the organic layer evaporated. The dihydride, m. p. 100°, was recovered almost quantitatively.

(*b*) A similar experiment with the dihydride, m. p. 130°, yielded 9 : 10-dimethylanthracene, m. p. 178°, alone or mixed with an authentic specimen.

Ultra-violet Absorption Spectra.—The curves were determined with a Beckman D U Spectrophotometer, using a constant spectral band width of 10 A. We are grateful to the Director of Chemistry, South Australian Government Department of Chemistry (S. D. Shield, Esq.), for permission to use the spectrophotometer.

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345. *Quantitative Analysis of Mixtures of Sugars by the Method of Partition Chromatography. Part V. Improved Methods for the Separation and Detection of the Sugars and their Methylated Derivatives on the Paper Chromatogram.*

By L. Hough, J. K. N. Jones, and W. H. Wadman.

The methylated sugars and uronic acids give specific colour reactions with various acidic spray reagents such as *p*-anisidine hydrochloride and aniline trichloroacetate, thus facilitating their detection and identification on the paper chromatogram. Other aids to the separation and identification of the sugars and their derivatives are discussed.

Partition chromatography has found general application in carbohydrate studies as a means of separating mixtures of reducing sugars, sugar alcohols, methylated sugars, and uronic acids

and their methylated derivatives. As a general method for the detection of reducing sugars on the paper chromatogram, Partridge employed an ammoniacal solution of silver nitrate (*Biochem. J.*, 1948, **42**, 238), the reducing sugars giving rise to discrete brown-black spots. Use of this reagent was later extended to the detection on the paper chromatogram of methylated sugars (Hirst, Hough, and Jones, *J.*, 1049, 928), polyhydric alcohols, and methyl glycosides of simple sugars (Hough, *Nature*, 1950, **165**, 400). Various specific spray reagents have been developed for the detection of individual classes of unsubstituted sugars. Their use depends on the formation of furfuraldehyde or a degradation product of furfuraldehyde by the action of an acid upon the sugar, and its subsequent reaction with an aromatic amine or phenol to give a coloured compound (cf. McGowan, *J.*, 1949, 777). For example, naphtharesorcinol and hydrochloric acid (Forsyth, *Nature*, 1948, **161**, 239), and naphtharesorcinol and trichloroacetic acid (Partridge, *loc. cit.*) have been utilised as selective spray reagents for the detection of raffinose, sucrose, and the ketohexoses. Chargaff, Levine, and Green (*J. Biol. Chem.*, 1948, **175**, 67) have used a solution of *m*-phenylenediamine dihydrochloride in 76% alcohol for the detection of the unsubstituted sugars, which give rise to coloured spots possessing a marked fluorescence in the ultra-violet light. Similarly Partridge (*Nature*, 1949, **164**, 443) records that with aniline phthalate in butanol the pentoses give a characteristic red colour, and that aldohexoses, methylaldopentoses, and hexuronic acids are readily detected as brown spots, ketohexoses giving little or no colour. We find that the methylated derivatives of aldohexoses, pentoses, ketohexoses, and uronic acids give excellent colours with aniline phthalate, trichloroacetate, or phosphate, as little as 1—5 μg. being detectable. Octoses and heptoses also yield brown colours. Partly methylated aldohexoses give rise to brown colours, sometimes with a tint of red, fully methylated aldohexoses giving a characteristic maroon colour. On the other hand, methylated aldopentoses give cherry-red colours. Methylated uronic acids give crimson-red colours of such high brilliance that they are readily distinguished. The rapid rate of formation of colour from methylated uronic acid derivatives indicates that they are easily degraded to furfuraldehyde. Methylated ketoses give green colours. The aniline salt reagent possesses many advantages over the ammoniacal silver reagent for the detection of the methylated sugars. It is equally, if not more, sensitive, giving characteristically coloured spots on a white background, which are stable for some considerable time. A large number of acidic spray reagents containing a variety of phenols and aromatic amines has been examined in order to find a universal reagent which will yield a specific colour with each particular class of sugar or methylated sugar. In this respect we find that solution of *p*-anisidine hydrochloride in *n*-butanol is very satisfactory, since with it aldohexoses give rise to a green-brown colour, ketohexoses a brilliant lemon-yellow colour, methyl aldopentoses an emerald-green colour, and uronic acids a cherry-red colour. Methylated aldohexoses furnish brown colours, sometimes with a tint of red, whereas methylated aldopentose derivatives give intense red colours. 2-Deoxyaldoses give pale-brown colours which appear as characteristic white fluorescent spots in ultra-violet light. The intensity of the coloured spots obtained with the reagent was considerably enhanced in ultra-violet light, thus providing a very sensitive means of detection. Diphenylamine trichloroacetate also serves to distinguish aldohexoses from aldopentoses, yielding with the former a brown and with the latter a purple colour. Furthermore, 2 : 3 : 4-trimethyl and 2 : 4-dimethyl xylose are readily distinguished from 2 : 3 : 5-trimethyl and 2 : 3-dimethyl arabinose since they respectively form an intense purple and a grey or faint purple colour. Methylated fructose derivatives yield a green colour with this reagent. Dimethylaniline is of little value for the detection of the simple sugars, but interesting results were obtained with the more fully methylated sugars. In this case, 2 : 3 : 5-trimethyl and 2 : 3-dimethyl arabinose gave an intense purple colour, whereas 2 : 3 : 4-trimethyl and 2 : 4-dimethyl xylose gave a light-brown colour. Characterisation of methylated arabofuranose derivatives and methylated xylopyranose derivatives on the paper chromatogram is therefore facilitated by the use of acidic sprays of dimethylaniline and diphenylamine. Methylated aldohexoses possessing free hydroxyl groups on $C_{(4)}$ of the sugar molecules, such as 2 : 3 : 5 : 6-tetramethyl, 2 : 3 : 6-trimethyl, and 2 : 3-dimethyl glucose also gave purple colours with dimethylaniline, whereas the other methylated aldohexoses gave little or no colour. Methylated fructose derivatives also gave purple colours.

α-Naphthylamine trichloroacetate is yet another general spray reagent, since aldohexoses and their partly methylated derivatives give a brown, fully methylated aldohexoses a red, ketohexoses a yellow, and aldopentoses a green colour. Once more a distinction between the methylated arabinoses and methylated xyloses was noted, since the latter gave intense green colours, whereas the former gave faint green colours; the colours appear purple in ultra-violet light.

Solutions of orcinol or resorcinol in butanol containing a little hydrochloric acid serve as

specific spray reagents for ketoses and their methylated derivatives since on heating only they yield red colours. Solutions of urea hydrochloride or anthraquinone and hydrochloric acid serve a similar purpose since the ketoses and their methylated derivatives yield intense brown-black spots whereas the other sugars yield little or no colour.

In general, the colours obtained with the acidic spray reagents described above improve when kept in a moist atmosphere for a short time or when the paper chromatograms are wetted. The brilliance and the definition of the coloured spots is considerably improved in ultra-violet light, and in some cases a change in colour is noted. The paper chromatograms may be washed with water, dried in a current of warm air, and preserved, but the colours fade somewhat. In practice, it is preferable to run sugars of known constitution alongside "unknowns" on the paper chromatogram, and to compare the rate of movement and the colours obtained with the various spray reagents in order to obtain some indication as to the identities of the "unknowns." We would emphasise that this evidence is not conclusive, however, and wherever possible it is necessary to separate the "unknowns" by partition chromatography on a column of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) and identify the sugar by measurement of physical constants and the formation of characteristic derivatives. Methylglycosides of the simple sugars may be detected by the use of the ammoniacal silver nitrate spray reagent (Hough, *Nature*, *loc. cit.*), which will detect as little as 5 μg. of the sugar glycoside. Methylglycosides may also be detected by the acidic sprays described above, but, in general, the reaction is rather weak and not as sensitive as the silver nitrate reagent. Polyhydric alcohols, which react with the ammoniacal silver nitrate reagent, do not give colours with the above acidic spray reagents and may therefore be distinguished. Colorimetric methods for the quantitative determination of sugars and, in particular, of their methylated derivatives, after separation on paper chromatograms or on columns of cellulose, have been explored, and will be described in an ensuing publication (with Mr. B. Clist).

Jermyn and Isherwood (*Biochem. J.*, 1949, **44**, 402) have recommended the use of solvent mixtures such as acetic acid–ethyl acetate–water, and pyridine–ethyl acetate–water, for the separation of the sugars on paper chromatograms. Hydrolysis of the ethyl acetate occurs, however, and consequently reproducible results are not readily obtained. It is also necessary to prepare fresh solvent for each separation. Rapid and efficient separations of sugars may be obtained, however, by using "miscible solvent mixtures" such as *n*-butanol–ethanol–water (4 : 1·1 : 1·9), and *n*-butanol–pyridine–water (3 : 1 : 1), which give reproducible results and can be used continuously. The R_F values of the carbohydrates and their derivatives can be adjusted by increasing the pyridine, ethanol, or water content of the mixture (thus increasing the R_F values) or by the addition of light petroleum to either solvent mixture (which depresses the R_F values). The separation of sugars is considerably accelerated by the use of Whatman No. 54 filter paper in place of No. 1 filter paper, but the sugars tend to trail on the former paper. No. 54 paper is of great value for the separation of di-, tri-, and oligo-saccharides. Uronic acids and their methylated derivatives may be separated satisfactorily in a miscible solvent mixture composed of *n*-butanol–glacial acetic acid–water (2 : 1 : 1); sugars also show excellent separations in this solvent mixture.

Separation of sugars and their methylated derivatives by partition chromatography on columns of cellulose has been described (Hough, Jones, and Wadman, *loc. cit.*). Although cellulose is best packed as the fine powder, an acid-treated cellulose, marketed as a fine powder, termed "hydrocellulose," forms excellent columns when packed as a slurry in acetone. Separations of sugars and their methylated derivatives on columns of "hydrocellulose" were as successful as those obtained previously on cellulose. This type of column can also be used to separate sugar glycosides and, in the Experimental section, the isolation of α- and β-methyl-L-rhamnopyranosides from the mixture produced on boiling L-rhamnose with methanolic hydrogen chloride is described.

After separation, identification of an unknown sugar may be facilitated by an examination, on the paper chromatogram, of the sugars produced on epimerisation with lime water. For example on epimerisation, either glucose, fructose, or mannose gives rise to a mixture of all three. Demethylation is also a useful aid to the characterisation of the methylated sugars (cf. Hess and Neumann, *Ber.*, 1935, **68**, 1371) since an unknown methylated sugar may be heated with hydrobromic acid at 100° for about 5 minutes, subsequent analysis of the demethylation products on the paper chromatogram giving a pattern by means of which the parent sugar may usually be identified by its R_F value and colour reaction. Tetramethyl glucose is readily converted into partly methylated glucose derivatives and glucose, trimethyl xylose is converted into xylose, and 2 : 6-dimethyl and 3-methyl galactose into galactose. Fructose derivatives, however,

are destroyed. This behaviour may result because of the more ready conversion of ketoses into ω-hydroxymethylfurfuraldehyde (cf. Haworth, Hirst, and Nicholson, *J.*, 1927, 1513).

The separation of sugars and their methylated derivatives on the paper chromatogram shows a marked improvement at elevated temperatures. At 37°, equilibrium is rapidly established in the chromatographic apparatus and, by use of *n*-butanol incompletely saturated with water as the mobile phase, rapid and efficacious separations have been achieved. In contrast to their behaviour on normal paper chromatograms, the sugars travel as small discrete spots of high concentration, which favour better colour formation with the acidic spray reagents described above. A mixture of galactose, arabinose, ribose, rhamnose, 2 : 4-dimethyl galactose, 2 : 3-dimethyl arabinose, 2 : 3 : 6-trimethyl glucose, and 2 : 3 : 4 : 6-tetramethyl glucose was completely separated on the paper chromatogram at 37° in 3 hours. Chromatography at 37° (on No. 54 paper) provides an excellent method for the separation of the di-, tri-, and oligo-saccharides.

Experimental.

Aniline Salts.—Crystalline specimens of aniline acetate, oxalate, phthalate, hydrochloride, phosphate and trichloroacetate were prepared in the usual manner. These were made up into (5·0, 0·5, and 0·1%) solutions in water, in glacial acetic acid, and in *n*-butanol, giving 9 solutions for each salt. Aqueous solutions of a representative selection of sugars and their methylated derivatives (see below), of 2·5 and 5·0% concentration respectively, were prepared. A spot of each was placed on a sheet of Whatman No. 1 filter paper and allowed to dry. A large number of these " test sheets " was prepared. In each case the spot diameter was approx. 5 mm., corresponding to 0·01 ml. of solution or 25 μg. of sugar and 50 μg. of methylated sugar. This may be regarded as an average value for the concentration of sugar or methylated sugar encountered in paper chromatography.

The following sugars and methyl sugars were used. Galactose and its 2 : 3 : 4 : 6-tetramethyl, 2 : 3 : 6-trimethyl, 4 : 6-, 2 : 6-, and 2 : 4-dimethyl, 2-methyl, and 2-deoxy-derivatives; glucose and its 2 : 3 : 4 : 6- and 2 : 3 : 5 : 6-tetramethyl, 2 : 3 : 6-trimethyl, 2 : 3-dimethyl, and 6-methyl derivatives; xylose and its 2 : 3 : 4-trimethyl, 2 : 4-dimethyl, and 2-methyl derivatives; arabinose and its 2 : 3 : 5-trimethyl, 2 : 3-dimethyl, and 2-methyl derivatives; galacturonic acid and its 2 : 3 : 4-trimethyl, 2 : 3-dimethyl, and 2-methyl derivatives; fructose and its 1 : 3 : 4-trimethyl and 1 : 3 : 4 : 5-tetramethyl derivatives; mannose and 4-methyl mannose; altrose, ribose, sorbose, tagatose, 2-deoxyribose, 2-deoxyallose, 2-deoxyrhamnose, glucoheptose, and D-*glucogal*octose. " Test sheets " were sprayed thinly and evenly with the various solution of the aniline salts described above. The papers were then heated at 100° in an electric oven fitted with a glass door and the development of the coloured spots observed. The sugars sprayed with the aniline salts in glacial acetic acid gave rise to colours of optimum intensity after about 3 minutes' heating. On the other hand, the papers sprayed with the aniline salts in *n*-butanol and in water required 10 minutes' heating, and the colours were inferior to those obtained in a medium of glacial acetic acid. Solutions (2·5%) of aniline phosphate, trichloroacetate, or phthalate in glacial acetic acid gave the best results, excellent colours being obtained with both the sugars and the methylated sugars. Any of these three reagents serves as a good general spray for the detection of the sugars or their methyl ethers on the paper chromatogram. Care must be taken to avoid over-heating the sprayed papers, otherwise the specific colours will be destroyed with the formation of brown spots in all cases. An excess of aniline has little effect on the brilliance of the coloured spots.

The above experiments were repeated with a variety of aromatic amines and phenols. The most useful general spray reagents proved to be : a solution (3%) of *p*-anisidine hydrogen chloride in *n*-butanol; a solution (2%) of dimethylaniline in glacial acetic acid containing trichloroacetic acid (5%); a solution (2%) of diphenylamine in *n*-butanol–methanol (1 : 1 v/v) containing trichloroacetic acid (5%); a solution (2%) of α-naphthylamine in *n*-butanol–methanol (1 : 1 v/v) containing trichloroacetic acid (5%). Solutions (3%) of orcinol or resorcinol in alcoholic hydrogen chloride (5%) gave specific red colours with ketoses, and similar solutions of urea and anthraquinone gave specific brown-black colours with the ketoses.

Demethylation.—The methylated sugar (5—10 mg.) in hydrobromic acid (48% w/w; 1 ml.) contained in a sealed glass tube is heated in the boiling water-bath for about 5 minutes. The contents are then immediately diluted with water (10 ml.). Portions of silver carbonate are added until the solution is neutral, whereafter a smaller quantity of decolorising charcoal is stirred in and the solution filtered. The last traces of silver are removed by the passage of hydrogen sulphide and filtration through a charcoal bed. The filtrate is concentrated to a thin syrup which is examined on the paper chromatogram. Typical results are as follows : (*a*) 2 : 3 : 4 : 6-tetramethyl glucose gave spots corresponding to trimethyl glucoses (R_G 0·84, 0·77), dimethyl glucose (R_G 0·50), monomethyl glucose (R_G 0·22), and glucose (R_G 0·10); (*b*) 2 : 3 : 5-trimethyl arabinose gave spots corresponding to dimethyl arabinoses (R_G 0·52, 0·73), monomethyl arabinoses (R_G 0·24, 0·31, 0·41), and arabinose (R_G 0·13); (*c*) 2 : 3 : 4-trimethyl xylose gave dimethyl xylose (R_G 0·67), monomethyl xylose, and xylose (R_G 0·17); (*d*) 3-methyl galactose gave galactose (R_G 0·08); (*e*) 4 : 6-dimethyl galactose gave galactose (R_G 0·08); (*f*) 2 : 3 : 4 : 6-tetramethyl galactose anilide, trimethyl rhamnose anilide, and 1 : 3 : 4 : 6-tetramethyl fructose were destroyed by the above procedure; demethylation products were not detected. The anilides and phenylhydrazones of the sugars, on being warmed with dilute hydrochloric acid, however, yield solutions containing the sugars, which can be separated and detected on the chromatogram in the usual manner.

Epimerisation.—The sugars are epimerised when kept at room temperature for a week or more in saturated solutions of calcium hydroxide. A more rapid epimerisation is achieved by heating the solutions at 100° for 10—15 minutes or at 37° for 24 hours. The solution is then neutralised by the addition of Amberlite resin IR.100. The best results are obtained at low temperatures. Glucose gave spots corresponding to glucose, mannose, and fructose. Galactose gave spots corresponding to galactose,

talose, and tagatose. Arabinose gave spots corresponding to arabinose, ribose, and riboketose. Sorbose gave spots corresponding to sorbose, idose, and galose. Rhamnose gave spots corresponding to rhamnose rhamnoketose, and glucomethylose. In all cases other degradation products were detected.

Partition Chromatography at 37° [with Mr. J. N. COUNSELL].—The usual type of chromatographic apparatus was used, precautions being taken to ensure that the container (a glass tank fitted with a thick plate-glass lid) was efficiently sealed. The under side of the glass lid and the upper edges of the tank were ground flat and "Apiezon *L*" grease was applied to the edges. Any leakage in the container results in a serious distortion of the solvent front as it advances over the paper. The whole apparatus was placed in a chamber thermostatically-controlled at 37°. *n*-Butanol saturated with water at room temperature was employed as the mobile phase. The apparatus was charged with solvent and allowed to stand for 24 hours before use. The results (see Table) show that the R_F values of the sugars are considerably increased and that rapid separations may be achieved on both No. 1 and No. 54 Whatman filter papers. A marked improvement in the definition of the spots was also noted. The rate of movement of a number of hexitols and disaccharides on the paper chromatogram was also improved. Chromatography at 37° for 16½ hours on No. 54 paper gave an excellent separation of the sugars; mannose, fructose, and arabinose were clearly distinguished, whereas at room temperature they are very difficult to separate.

Distance (cm.) *from the centre of the sugar spot to the starting point and* R_F *values.**

Whatman filter paper:	No. 1.	No. 1.	No. 54.		No. 54.
Temp. and duration of chromatography:	17°; 16½ hrs.	37°; 6 hrs.	37°; 3 hrs.		37°; 16½ hrs.
Distance from solvent front to the starting line (cm.):	front 29·1.	front 20·4.	front 30·7.		†
Galactose	1·6 (0·055)	2·35 (0·115)	3·1 (0·102)		12·1 (0·102 ‡)
Glucose	—	—	—		13·3 (0·111)
Mannose	—	—	5·0 (0·163)		18·7 (0·156)
Fructose	—	—	4·9 (0·160)		19·8 (0·165)
Arabinose	2·7 (0·093)	3·9 (0·192)	5·5 (0·178)		20·4 (0·177)
Ribose	4·4 (0·151)	5·7 (0·278)	8·1 (0·265)		28·7 (0·240)
Rhamnose	6·0 (0·206)	8·0 (0·359)	10·5 (0·342)	Sorbitol	15·3 (0·124)
2 : 4-Dimethyl galactose	—	9·35 (0·457)	13·7 (0·446)	Mannitol	15·9 (0·129)
2 : 3-Dimethyl arabinose	11·4 (0·392)	13·1 (0·641)	19·9 (0·650)	Dulcitol	15·3 (0·124)
2 : 3 : 6-Trimethyl glucose	16·4 (0·563)	15·3 (0·748)	23·1 (0·752)	Turanose	6·6 (0·055)
2 : 3 : 4 : 6-Tetramethyl glucose	21·5 (0·738)	17·45 (0·854)	26·3 (0·857)	Sucrose	6·1 (0·051)
				Melibiose	12·8 (0·107)

* R_F values are given in parentheses.
† The solvent front reached the bottom of the paper and was allowed to drip off.
‡ This R_F value was assumed, and the R_F values of the other materials on the chromatogram were calculated by proportion.

Separation of α- and β-Methyl-L-rhamnopyranoside.—L-Rhamnose (10 g.; anhydrous) was boiled with methanolic hydrogen chloride (250 c.c.; 2%) for 12 hours. The cooled solution was neutralised with silver carbonate and filtered, and the filtrate concentrated to a syrup (10·6 g.). The syrup was dissolved in *n*-butanol (7 c.c.) two-thirds saturated with water, and transferred to the top of a column (50 cm. long, 6 cm. diam.) of "hydrocellulose," and the glycosides were separated in the manner described by Hough, Jones, and Wadman (*loc. cit.*), with butanol–water as the mobile phase. The fractions containing the glycosides were examined on the filter-paper chromatogram (Hough, *loc. cit.*). After selection of the appropriate fractions, subsequent concentration gave α- (9·1 g.), $[\alpha]_D^{20}$ −63° (water), R_{Gl} 0·53, and β-methyl-L-rhamnopyranoside (0·9 g.), m. p. 139°, $[\alpha]_D^{20}$ +94° (water), R_{Gl} 0·42.

We thank Professor E. L. Hirst, F.R.S., for his interest and advice, and Professor C. S. Hudson for the gift of heptose and octose sugars. One of us (W. H. W.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

THE UNIVERSITY, BRISTOL.

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346. *Stereochemical Studies of Olefinic Compounds. Part II.* Ring Scission of 2-1′-Halogenoalkyltetrahydrofurans and 3-Halogeno-2-alkyltetrahydropyrans as a Route to Alk-4-en-1-ols of Known Configuration and as a Method of Chain Extension by Five Methylene Groups.*

By Leslie Crombie and Stanley H. Harper.

The preparation and ring scission of 2-1′-bromoalkyltetrahydrofurans and 3-chloro-2-alkyltetrahydropyrans are investigated as routes to alk-4-en-1-ols and thence, by catalytic reduction, as a means of chain extension by five methylene groups. Although 2-1′-hydroxyethyltetrahydrofuran is readily prepared, conversion into a halide in acceptable yield is difficult. Ring scission of the bromide with sodium gives a moderate yield of *n*-hex-4-en-1-ol, shown to be predominately *trans*, though the infra-red absorption indicates the presence of some of the *cis*-isomer.

The same objective is reached more effectively from 3-chloro-2-alkyltetrahydropyrans. 2 : 3-Dichlorotetrahydropyran and methylmagnesium bromide give *cis*- and *trans*-3-chloro-2-methyltetrahydropyran, separable by distillation but both converted by ring scission into exclusively *trans*-*n*-hex-4-en-1-ol in high yield. Configurations are assigned by comparison with authentic *cis*- and *trans*-*n*-hex-4-en-1-ol, made by catalytic semi-hydrogenation and by reduction by sodium in liquid ammonia, respectively, of *n*-hex-4-yn-1-ol, through mixed melting points of derivatives, and through the infra-red absorption of the alcohols. *n*-Hept-, *n*-oct-, and *n*-non-4-en-1-ols are also prepared by this method and assigned the *trans*-configuration from their infra-red absorption.

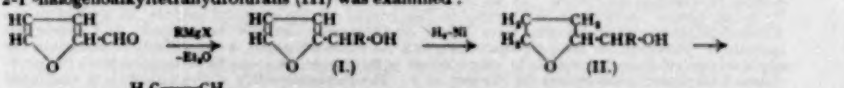
The ring scission of 3-chloro-2-alkyltetrahydropyrans is believed to provide a general route to *trans*-alk-4-en-1-ols.

When a β-halogeno-ether is treated with one of the more electro-positive metals, halogen elimination and scission of the β-carbon–oxygen bond occurs with formation of an olefin and a metal alkoxide: $R{\cdot}O{\cdot}CH_2{\cdot}CH_2X + 2M \longrightarrow R{\cdot}OM + CH_2{:}CH_2 + MX$

Thus reaction of 2-phenoxyethyl bromide with magnesium or sodium gives ethylene and the phenoxide (Grignard, *Compt. rend.*, 1904, **138**, 1048; Wohl and Berthold, *Ber.*, 1910, **43**, 2175); Boord and his co-workers (*J. Amer. Chem. Soc.*, 1930, **52**, 651, 3396; 1931, **53**, 1505, 2427; 1932, **54**, 751; 1933, **55**, 3293, 4930) generalised the reaction with zinc as a method of preparing olefinic hydrocarbons of the types $RCH{:}CH_2$, $RCH{:}CHR'$, $RR'C{:}CH_2$, and $RR'C{:}CHR''$; and 2-bromoethyl alkyl ethers with magnesium give ethylene and the bromomagnesium alkoxide (Tallman, *ibid.*, 1934, **56**, 126). When the ether is cyclic the hydroxyl and the ethylenic link are produced within the same molecule by ring scission. Thus tetrahydrofurfuryl chloride or bromide with magnesium or sodium in ether gives *n*-pent-4-en-1-ol in high yield (Paul, *Bull. Soc. chim.*, 1933, [iv], **53**, 424; 1935, [v], **2**, 745; Paul and Normant, *ibid.*, 1943, [v], **10**, 484; *Org. Synth.*, 1945, **25**, 84; Robinson and Smith, *J.*, 1936, 195), and 3-bromotetrahydrofuran is attacked by lithium in ether to give *n*-but-3-en-1-ol (Amstutz, *J. Org. Chem.*, 1944, **9**, 310).

It appeared that ring scission of cyclic β-halogeno-ethers should be capable of extension to provide routes to various ethylenic alcohols of known configuration and, by subsequent catalytic hydrogenation, afford methods for the extension of carbon chains by several methylene groups at a time. The unit added would be terminated by a functional group suitable for a repetition of the process or for other standard reactions. In this and the following paper a study of three such ring scissions, with particular reference to the stereochemistry of the products, is presented. Examples of the use of these reactions have already been given by us (Crombie and Harper, *Nature*, 1949, **164**, 534, 1053; *J.*, 1950, 1152).

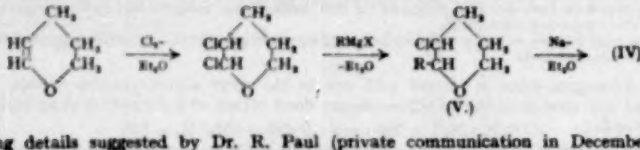
When this work was started (1947), no satisfactory procedure for the preparation of tetrahydrofurfuraldehyde was available (cf. Owen, *Ann. Reports*, 1945, **42**, 152)—though it has since been made readily available by the work of Bremner, Coats, Robertson, and Allan (*J.*, 1949, S 25)—and the following route to alk-4-en-1-ols (IV) through the ring scission of 2-1′-halogenoalkyltetrahydrofurans (III) was examined:



* "' Leaf Alcohol ' and the Stereochemistry of the *cis*- and *trans*-*n*-Hex-3-en-1-ols and *n*-Pent-3-en-1-ols " (Crombie and Harper, *J.*, 1950, 873) is regarded as Part I of this series.

Furfuraldehyde was converted into 2-1′-hydroxyethylfuran (I; R = Me) by the Grignard reaction (Peters and Fischer, *J. Amer. Chem. Soc.*, 1930, **52**, 2079; Paul, *Bull. Soc. chim.*, 1937, [v], **4**, 846) and thence by hydrogenation over Raney nickel into 2-1′-hydroxyethyltetrahydrofuran (II; R = Me) in high yield. Prolongation of the reduction time led to a lower yield through the formation of higher-boiling material, probably diols formed by hydrogenolysis of the furan ring. Conversion of this carbinol into a halide was unexpectedly difficult, for thionyl chloride, anhydrous hydrogen chloride, and phosphorus and iodine gave very poor yields of impure halides, while phosphorus tribromide gave only 34% of the bromide (III; R = Me, X = Br), which was difficult to purify. This bromide reacted vigorously with sodium to give a non-homogeneous n-hex-4-en-1-ol (IV; R = Me) (evidence is given below that this is the *trans*-alcohol, probably in admixture with the *cis*-isomer). In view of the mediocre yields and the apparent impurity of the product this route was unsatisfactory. At this time Paul and Riobé (*Compt. rend.*, 1947, **224**, 474) recorded a similar failure to convert 2-1′-hydroxy-n-amyltetrahydrofuran (II; R = Bu^n) satisfactorily into a halide, but reached the same objective, n-non-4-en-1-ol (IV; R = Bu^n), by the ring scission of 3-chloro-2-n-butyltetrahydropyran (V; R = Bu^n), which Paul (*ibid.*, 1944, **218**, 122) had earlier reported, though without details, as obtained from 2 : 3-dichlorotetrahydropyran and n-butylmagnesium chloride.

We therefore turned our attention to the following as a route to alk-4-en-1-ols:



Following details suggested by Dr. R. Paul (private communication in December, 1947) dihydropyran (1 mol.) in ether was chlorinated at 0° and without isolation the 2 : 3-dichlorotetrahydropyran was added to the appropriate Grignard reagent (1·5 mols.) (R = Me, Et, Pr^n, and Bu^n); this provides a general route to 3-chloro-2-alkyltetrahydropyrans (V). In further experiments with Mr. J. H. Brookman we have found it possible to reduce the excess of Grignard reagent without causing resinification or seriously diminishing the yield, if vigorous stirring is maintained towards the end of the addition when solid tends to separate. If local concentrations of 2 : 3-dichlorotetrahydropyran are set up resinification occurs. We have not found it profitable to reduce the proportion of alkyl halide below 1·1—1·2 mols., since the formation of the Grignard reagent is not quantitative and contamination of the product with unchanged 2 : 3-dichlorotetrahydropyran is undesirable. When methylmagnesium iodide (1 mol.) was added to 2 : 3-dichlorotetrahydropyran (1 mol.) in ether resinification occurred and scarcely any of the desired product (V; R = Me) was obtained.

Riobé (*ibid.*, 1947, **225**, 334) showed that the 3-chloro-2-alkyltetrahydropyrans (V; R = Me, Et, and Pr^n) so obtained are separable into lower- and higher-boiling isomeric forms. From the relative values of the physical constants of the pairs of isomers he concluded that the former is *trans* and the latter *cis*. These configurations are consistent with the relative speeds of reaction with ethanolic sodium ethoxide and with the products formed on treatment with potassium hydroxide in diethylene glycol (*ibid.*, 1948, **226**, 1625; *Ann. Chim.*, 1949, **4**, 593).* Riobé stated that on ring scission the *cis*- and the *trans*-isomer gave the same alcohol (IV), the evidence being that neither the ethylenic alcohols nor their acetates could be fractionated by distillation into isomers. Since the boiling points of such *cis*- and *trans*-olefinic alcohols (cf. Crombie and Harper, Part I, *J.*, 1950, 873) are generally very close, fractionation would need to be very

* In his earliest paper Riobé designated the lower-boiling (*trans*-)isomer the α- and the higher-boiling (*cis*-)isomer the β-form. In his later papers he reversed this nomenclature without comment. To avoid further confusion it is desirable to discontinue the use of Greek prefixes, as applied to the 3-chloro-2-alkyltetrahydropyrans, since actual configurations can now be assigned with reasonable certainty. However, for the purposes of this and the following paper, it is necessary to designate the alcohols derived from the *trans*-, by ring scission with sodium, as α and those derived from the *cis*-3-chloro-2-alkyltetrahydro-pyrans (or -furans) as β. The stereochemistry of these alcohols is elucidated later in these papers and this notation too then becomes redundant. Paul and Tchelitcheff (*Bull. Soc. chim.*, 1948, [v], **15**, 1199) have separated the isomeric 3-chloro-2-n-hexyltetrahydropyrans and assigned the *cis*-configuration to the lower-boiling isomer; on the basis of the Auwers–Skita generalisations we believe this to be incorrect.

[*Added in proof, May 15th*, 1950.] Dr. R. Paul (private communication) concurs with us that the assignments of configuration made by Paul and Tchelitcheff should be reversed.

refined to be a convincing test. We have therefore investigated the homogeneity and the stereochemistry of the alcohols formed in this reaction.

Fractional distillation of crude 3-chloro-2-methyltetrahydropyran yielded the higher- and the lower-boiling isomer, whose physical properties differ somewhat from those reported by

TABLE I.

3-Chloro-2-methyltetrahydropyran.	B. p.	d_4^{20}.	n_D^{20}.	$[R_L]_D$. Found.	Calc.	Ref.
trans-	134°; 51°/18 mm.	1·071	1·4551	34·09	34·22	1
	56°/23 mm.	1·058	1·4543	34·43	34·22	2
cis-	172°; 66°/18 mm.	1·091	1·4626	33·97	34·22	1
	72°/23 mm.	1·090	1·4646	34·09	34·22	2

[1] Crombie and Harper, this paper. [2] Riobé, *Ann. Chim.*, 1949, **4**, 593.

Riobé (Table I). On the assumption that the Auwers–Skita generalisations are applicable to tetrahydropyrans, we agree with Riobé's assignment of configurations. During distillation of the precursory 2 : 3-dichlorotetrahydropyran we observed no appreciable spread of boiling point; we believe that this consists of one geometrical form only, since addition of halogens to a double bond, here *cis*, is known to occur *trans* and would give *trans*-2 : 3-dichlorotetrahydropyran (cf. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, p. 147; Raphael, *J.*, 1949, S 44, and references cited therein). When therefore this 2 : 3-dichlorotetrahydropyran reacts with the Grignard reagent, $C_{(2)}$ becomes planar owing to the formation of a carbonium ion (S_N1 mechanism), and both *cis*- and *trans*-3-chloro-2-alkyltetrahydropyran are produced.

Subjecting *cis*- and *trans*-3-chloro-2-methyltetrahydropyran separately to ring scission we observed that the *cis*- reacted more vigorously with sodium than did the *trans*-isomer. The α- and β-*n*-hex-4-en-1-ol had nearly identical physical properties (Table II) and gave identical 1-naphthyl- and 4-diphenylyl-urethanes. Furthermore, conversion of (α + β)-*n*-hex-4-en-1-ol, made by ring scission of the mixed *cis*- and *trans*-3-chloro-2-methyltetrahydropyrans, into *n*-hept-5-enoic acid,[4] through the *n*-hex-4-enyl bromide and carboxylation of the derived Grignard reagent, gave an acid which from the purity of its derivatives was homogeneous (to be reported later). We conclude, in agreement with Riobé, that this ring scission gives a single stereoisomer of *n*-hex-4-en-1-ol. We have also prepared (α + β)-*n*-hept-, (α + β)-*n*-

TABLE II.

n-Hex-4-en-1-ol.	B. p.	n_D^{20}.	1-Naphthylurethane, m. p.	4-Diphenylylurethane, m. p.
α-	158°	1·4403	73°	93—94°
β-	159	1·4402	73	92—93
cis-	158—159	1·4420	74—75	77·5
trans-	158	1·4402	72	93

oct-, and (α + β)-*n*-non-4-en-1-ol, by ring scission of the appropriate 3-chloro-2-alkyltetrahydropyran (V; R = Et, Pr^n, and Bu^n) and have observed no indications of the presence of more than one stereoisomer.

To elucidate the configuration of the isomer formed in the ring scission we have prepared *cis*- and *trans*-*n*-hex-4-en-1-ol by unambiguous routes. (α + β)-*n*-Hex-4-en-1-ol was brominated in ether below 0° and the 4 : 5-dibromohexanol dehydrobrominated by sodamide in liquid ammonia, to yield *n*-hex-4-yn-1-ol, characterised as its 1-naphthylurethane. From this hexynol, authentic *cis*-*n*-hex-4-en-1-ol was prepared by semi-hydrogenation over palladium–calcium carbonate at room temperature. This procedure is known to give a *cis*-double bond (Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 90; Part I, *loc. cit.*). Reduction of the hexynol with sodium in liquid ammonia, which is known to proceed by *trans*-addition (Campbell and Campbell, *loc. cit.*; Sondheimer, *J.*, 1950, 877; Part I, *loc. cit.*), yielded *trans*-*n*-hex-4-en-1-ol. These alcohols were characterised as their 1-naphthyl- and 4-diphenylyl-urethanes (Table II), and mixed melting points established the identity of the α- and the β-*n*-hex-4-en-1-ol with the *trans*-isomer.

The assignment of the *trans*-configuration to the alcohol formed by ring scission is supported by infra-red absorption measurements. The spectra of α-, β-, and *trans*-*n*-hex-4-en-1-ol (Figs. 1—3 respectively) are closely similar and differ markedly from that of the *cis*-isomer

[4] In this and succeeding papers we use Geneva numbering for carboxylic acids.

(Fig. 4). Strong absorption at 10·3 μ. is characteristic of the *trans*-forms (*cf.* Part I, *loc. cit.*), absorption here being very much weaker for the *cis*-form. In the spectrum of *cis*-n-hex-3-en-1-ol (*loc. cit.*, Fig. 1) there is marked absorption at 11·5 μ., but careful examination has failed to reveal a corresponding peak in that of *cis*-n-hex-4-en-1-ol; the latter has however characteristic absorption at 9·65 μ. The spectra of the α- and β-alcohols give no indication of the presence of *cis*-isomer. In particular the relative intensities of the 9·4-μ. (primary hydroxyl) and the 10·3-μ. ("*trans*") band correspond closely with those for the pure *trans*-isomer; any *cis*-isomer

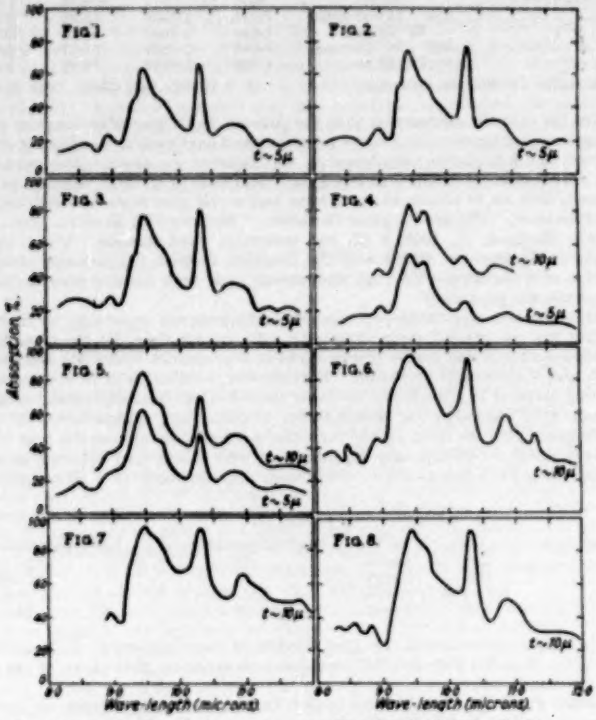


Fig. 1.—α-n-*Hex*-4-*en*-1-*ol*.
Fig. 2.—β-n-*Hex*-4-*en*-1-*ol*.
Fig. 3.—trans-n-*Hex*-4-*en*-1-*ol*.
Fig. 4.—cis-n-*Hex*-4-*en*-1-*ol*.
Fig. 5.—n-*Hex*-4-*en*-1-*ol from ring scission of* 2-1′-*bromoethyltetrahydrofuran*.
Fig. 6.—(α + β)-n-*Hept*-4-*en*-1-*ol*.
Fig. 7.—(α + β)-n-*Oct*-4-*en*-1-*ol*.
Fig. 8.—(α + β)-n-*Non*-4-*en*-1-*ol*.

should be easily detected by decrease in absorption at 10·3 μ. Thus on chemical and spectroscopic evidence the product of the ring scission of both *cis*- and *trans*-3-chloro-2-methyltetrahydropyran is *trans*-n-hex-4-en-1-ol, free from any detectable quantity of the *cis*-isomer. The infra-red absorption spectra of (α + β)-n-hept-, (α + β)-n-oct-, and (α + β)-n-non-4-en-1-ol (Figs. 6—8 respectively) all exhibit the strong "*trans*" peak at 10·3 μ. Reference samples of the corresponding authentic *cis*- and *trans*-alcohols have not been prepared, but from the spectroscopic evidence coupled with the apparent chemical homogeneity, we conclude that these too are pure *trans*-isomers.

In view of the exclusive formation of the *trans*-alcohol in this ring scission we have re-examined the specimen of n-hex-4-en-1-ol obtained by ring scission of 2-1′-bromoethyl-

tetrahydrofuran. The melting point of its 4-diphenylylurethane was not sharp but was raised on admixture with that of the authentic *trans*-derivative. The alcohol thus appears to be largely but not entirely *trans*-n-hex-4-en-1-ol. This view is supported by the infra-red spectrum (Fig. 5) which bears a general similarity to that of the *trans*-alcohol (Fig. 3) but differs in two important features. First, there are signs of a new absorption maximum appearing at ~9·7 μ., this being more distinct than the inflexion which occurs in this region for the *trans*-isomer. Secondly, the intensity of absorption of the 10·3-μ. ("*trans*") band relative to that of the 9·4-μ. (primary hydroxyl) peak is markedly reduced. Both these observations suggest that the contaminant is *cis*-n-hex-4-en-1-ol and that the ring scission of 2-1′-bromoethyltetrahydrofuran gives a mixture of *cis*- and *trans*-n-hex-4-en-1-ols.

We reserve discussion of the mechanism of these ring scissions until the following paper.

Experimental.

Microanalyses, apart from the halogen determinations, are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. Infra-red absorption spectra were determined by one of us (L. C.) with a Grubb Parsons spectrometer coupled to a Brown recorder, using the pure liquids in a cell of 5—10-μ. thickness (not constant). The spectra were measured over the range 6—15 μ. but only the most important portion (8—12 μ.) is reproduced. We are indebted to Dr. W. C. Price for this facility.

2-1′-Hydroxyethylfuran.—Freshly distilled furfuraldehyde (240 g., 1·0 mol.) was added dropwise during 4 hours to the vigorously stirred ice-cold Grignard reagent prepared from methyl iodide (444 g., 1·25 mols.) and magnesium (30 g.) in dry ether (900 ml.). Next day the product was treated with iced water and the aqueous slurry thrice further extracted with ether. The ethereal extract was washed with aqueous sodium hydrogen sulphite and then water, and dried (K_2CO_3). A few drops of aniline were added, the ether was removed, and the residue distilled to give 2-1′-hydroxyethylfuran (182 g., 65%), b. p. 80·5°/21 mm., n_D^{20} 1·4794. Peters and Fischer (*J. Amer. Chem. Soc.*, 1930, **52**, 2079) record b. p. 76—77°/23 mm., n_D^{20} 1·4785. This carbinol was particularly sensitive to acids and was therefore stored in the presence of a little base.

2-1′-Hydroxyethyltetrahydrofuran.—2-1′-Hydroxyethylfuran (70·5 g.) in ethanol (200 ml.) was hydrogenated at 100°/125 atm. in a metal autoclave fitted with a magnetically operated agitator in the presence of Raney nickel (7 g.). After 3 hours the reduction was stopped, the suspension filtered, and the ethanol evaporated under a column. Distillation of the residue gave 2-1′-hydroxyethyltetrahydrofuran (65 g., 89%), b. p. 75—77°/20 mm., n_D^{20} 1·4480 (Found: C, 62·3; H, 10·15. Calc. for $C_6H_{12}O_2$: C, 62·1; H, 10·3%), which possessed a mushroom-like odour. Paul (*Bull. Soc. chim.*, 1937, [v], **4**, 946) records b. p. 71°/16 mm., n_D^{15} 1·4500. In another reduction, when the hydrogenation was continued for 18 hours at 100°, the yield dropped to 80% and there was a larger proportion of high-boiling residue.

Attempts to Prepare 2-1′-Halogenoethyltetrahydrofurans.—Thionyl chloride and pyridine (cf. *Org. Synth.*, 1945, **25**, 84), even at −20°, caused resinification and gave only a trace of the required chloride, as did anhydrous hydrogen chloride.

Red phosphorus (0·55 g.) was mixed with 2-1′-hydroxyethyltetrahydrofuran (5·8 g.), and then iodine (6·35 g.) added in portions. The mixture became hot and the reaction was completed at 100° during 1 hour. The product was diluted with ether and filtered through glass wool, and the filtrate washed with aqueous potassium hydroxide. After drying and evaporation the residue was distilled at 3 mm. to give fractions: b. p. 45—78°, n_D^{20} 1·4845 (1·7 g.) (Found: I, 45·7); b. p. 78—100°, n_D^{20} 1·5304 (0·9 g.) (Found: I, 58·1); and b. p. 100—103°, n_D^{20} 1·5540 (1·2 g.) (Found: I, 62·1. Calc. for $C_6H_{11}OI$: I, 56·2%). Much decomposition occurred on attempting to distill the crude iodide at 45 mm.

2-1′-Hydroxyethyltetrahydrofuran (27 g.), mixed with pyridine (3 ml.), was added dropwise slowly to a mixture of phosphorus tribromide (22·4 g.) and pyridine (1 ml.) kept at 0° (cf. Robinson and Smith, *J.*, 1936, 195). After 48 hours at room temperature the product was distilled off under vacuum and had b. p. 74°/21 mm. to 140°/45 mm. This crude bromide was twice fractionated by distillation at 14 mm. to give fractions: b. p. below 68°, n_D^{20} 1·4712 (0·7 g.); b. p. 68—70°, n_D^{20} 1·4744 (4·4 g.) (Found: Br, 45·5%); b. p. 70—80°, n_D^{20} 1·4742 (2·0 g.); b. p. 80—90°, n_D^{20} 1·4740 (3·8 g.); b. p. 90—100°, n_D^{20} 1·4740 (4·0 g.) (Found: Br, 46·4. Calc. for $C_6H_{11}OBr$: Br, 44·7%). Repetition of this distillation gave no better results. In another experiment the carbinol (13·5 g.) was added during 30 minutes to phosphorus tribromide (11·2 g.) kept at −5°, in the absence of pyridine. The product was worked up following the procedure of Gerrard (*J.*, 1945, 848) and distilled at 18 mm. to give fractions: b. p. 46—70°, n_D^{20} 1·4842 (1·4 g.); b. p. 70—80°, n_D^{20} 1·4791 (1·4 g.); and b. p. 80—95°, n_D^{20} 1·4810 (2·1 g.).

Ring Scission of 2-1′-Bromoethyltetrahydrofuran.—The bromide (10·0 g.; b. p. 68—100°/14 mm.) in anhydrous ether (25 ml.) was added dropwise to a stirred suspension of powdered sodium (3·5 g., well rinsed with ether to remove xylene) in anhydrous ether (25 ml.). An exothermic reaction ensued, sufficient to cause gentle refluxing of the ether, whilst the sodium became purple. When reaction had finished water was added, and the ethereal layer separated, washed, and dried ($MgSO_4$). Careful removal of the ether and distillation of the residue gave a fraction, b. p. 130—160°, n_D^{20} 1·4426 (3·0 g., 54%). This crude n-hex-4-en-1-ol was redistilled at 11 mm. to give three fractions: (i) b. p. 52—54°, n_D^{20} 1·4408 (0·6 g.); (ii) b. p. 54—59°, n_D^{20} 1·4401 (0·5 g.); and (iii) b. p. 59—66°, n_D^{20} 1·4442 (0·8 g.). Similar results were obtained in other experiments [Found (for a sample redistilled at atmospheric pressure): C, 72·3; H, 11·5. Calc. for $C_6H_{12}O$: C, 71·9; H, 12·1%].

After 2 years, fraction (iii) was redistilled; it then had b. p. 159°, n_D^{20} 1·4413. Its 4-diphenylylurethane had m. p. 81—84° after two crystallisations from light petroleum (b. p. 60—100°); when admixed with authentic *trans*-n-hex-4-en-1-yl 4-diphenylylurethane (see below; m. p. 93°) it had m. p. 82—86° and admixed with authentic *cis*-derivative (m. p. 76°) had m. p. 75—80°.

3-Chloro-2-methyltetrahydropyran.—Dihydropyran (168 g.) in dry ether (400 ml.) was kept between

0° and 5°, and dried chlorine passed into the solution until it acquired a green tinge due to excess of chlorine (*ca.* 2·5 hours). Excess of chlorine was then removed by the dropwise addition of dihydropyran until the solution of 2 : 3-dichlorotetrahydropyran (310 g., 1·0 mol.) was again colourless. Meanwhile methylmagnesium bromide (1·5 mols.) was prepared in dry ether (800 ml.) from magnesium (72 g.) and gaseous methyl bromide. This reagent was cooled in an ice-bath and well stirred by means of a Hershberg wire stirrer while the 2 : 3-dichlorotetrahydropyran solution prepared above was added dropwise. After storage at room temperature, usually overnight, the excess of methylmagnesium bromide was decomposed by the cautious addition of cold ammonium chloride solution, with stirring and external cooling. Concentrated hydrochloric acid (98 ml.) was then added and the ethereal layer separated and dried (K_2CO_3). The ether was removed, and the residue distilled to give, after elimination of lower-boiling material, the mixed *cis*- and *trans*-3-chloro-2-methyltetrahydropyrans (164 g., 61%), b. p. 150—175° (mainly), n_D^{20} 1·4594. This mixture was fractionally distilled, first at 13 mm. and then at atmospheric pressure, through a 50 × 1·5-cm. helices-packed column with variable take-off and electrically heated jacket, to give the lower-boiling *trans*- and the higher-boiling *cis*-isomer (see Table I). The *cis*-form darkened when kept, whereas the *trans*-form remained colourless.

Ring Scission of 3-*Chloro*-2-*methyltetrahydropyran.*—Sodium (144 g., 2·2 g.-atoms) was powdered under xylene, then thoroughly rinsed with dry ether, and covered with this solvent (1 l.). A little 3-chloro-2-methyltetrahydropyran (*cis*- + *trans*-) was added and the suspension stirred with a Hershberg wire stirrer until reaction commenced as shown by the surface of the sodium assuming an indigo-blue colour and by refluxing of the ether. The remaining 3-chloro-2-methyltetrahydropyran (380 g. in all, 1 mol.) was now added dropwise, so that steady refluxing was maintained. The thick blue suspension was stirred for a further 2 hours and then kept at room temperature overnight. Next day ice and water were cautiously added. The ethereal layer was separated and the aqueous layer further extracted with ether. After being washed and dried (Na_2SO_4), the ether was removed under a column from the combined ethereal extracts, and the residue distilled to give (*trans*-)*n*-hex-4-en-1-ol (230 g., 82%), b. p. 68·5°/15 mm., n_D^{20} 1·4403.

In like manner *trans*-3-chloro-2-methyltetrahydropyran (18 g.) gave α-*n*-hex-4-en-1-ol (11·6 g., 87%), b. p. 158°, n_D^{20} 1·4403, characterised as the 1-naphthylurethane, needles [from light petroleum (b. p. 40—60°)], m. p. 73°, and as the 4-diphenylylurethane, clumps of short needles [from light petroleum (b. p. 80—100°)], m. p. 93—94°.

Similarly *cis*-3-chloro-2-methyltetrahydropyran (17 g.) with sodium (6·5 g.) gave β-*n*-hex-4-en-1-ol (9·9 g., 78%), b. p. 159°, n_D^{20} 1·4402, characterised as the 1-naphthylurethane (needles), m. p. 73°, and as the 4-diphenylylurethane (clumps of needles), m. p. 92—93°. Neither the 1-naphthyl- nor the 4-diphenylyl-urethane of the α- and β-alcohols showed depressions of the m. p. when mixed, or when mixed with the corresponding derivatives of authentic *trans*-*n*-hex-4-en-1-ol (see below). These derivatives were obtained pure more readily (1 or 2 crystallisations) than those of *trans*-*n*-hex-4-en-1-ol obtained by reduction of *n*-hex-4-yn-1-ol with sodium in liquid ammonia.

n-Hex-4-yn-1-ol.—Bromine (99 g.) was added slowly to the (*trans*-)*n*-hex-4-en-1-ol (61·5 g.), obtained by ring scission of *cis*- + *trans*-3-chloro-2-methyltetrahydropyran, diluted with an equal volume of anhydrous ether, at <10° (external cooling). When addition was complete (2—3 hours), the ether was sucked off by a water-pump at room temperature from the crude *erythro*-4 : 5-dibromohexanol. To a solution of sodamide [from sodium (70 g.) and liquid ammonia (2 l.) in the presence of ferric nitrate (cf. Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120)], the 4 : 5-dibromohexanol was added rapidly, with cooling in alcohol–solid carbon dioxide. After 3 hours' stirring the flask was removed from the cooling bath, ether (100 ml.) added, and the ammonia allowed to evaporate overnight. Next day water was added and the alcohol removed by 5 extractions with ether. The extracts were washed with dilute acid and then water and dried, and the ether removed under a column. Distillation of the brown residue gave the crude alcohol (25 g., 41%), b. p. 160—178°, which was refractionated to give *n-hex-4-yn-1-ol* (19·6 g., 31%), b. p. 165—168°, n_D^{20} 1·4586 (Found: C, 73·35, 73·4; H, 10·5, 10·55. $C_6H_{10}O$ requires C, 73·4; H, 10·25%). The 1-*naphthylurethane*, which crystallised from light petroleum (b. p. 40—60°), had m. p. 82° (Found: C, 76·25; H, 6·45; N, 5·55. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·25%).

trans-*n-Hex-4-en-1-ol.*—*n*-Hex-4-yn-1-ol (5·0 g.) was added dropwise to a stirred solution of sodium (5 g.) in liquid ammonia (250 ml.), cooled in alcohol–solid carbon dioxide. The alcohol was washed in with a little ether, and the mixture stirred for a further 90 minutes, whereafter solid ammonium chloride was added cautiously until the blue colour was discharged. The solution was covered with ether (15 ml.), and the ammonia allowed to evaporate overnight. Next day water (50 ml.) and more ether (10 ml.) were added, and the ethereal layer was separated. The aqueous layer was extracted 3 times with ether and the combined ethereal extracts were washed with 10% sulphuric acid, then water, and dried. Removal of the ether through a column and distillation of the residue gave trans-*n-hex-4-en-1-ol* (3·95 g., 72%), b. p. 158°, n_D^{20} 1·4402 (Found: C, 71·35; H, 11·95. $C_6H_{12}O$ requires C, 71·9; H, 12·1%). The 1-*naphthylurethane*, forming needles from light petroleum (b. p. 40—60°) after 4 crystallisations, had m. p. 72° (Found: C, 75·5; H, 6·9; N, 5·55. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%), whilst the 4-*diphenylylurethane* formed clumps of short needles [from light petroleum (b. p. 80—100°)], having m. p. 93° (Found: C, 77·0; H, 7·25. $C_{19}H_{21}O_2N$ requires C, 77·25; H, 7·25%).

cis-*n-Hex-4-en-1-ol.*—*n*-Hex-4-yn-1-ol (5·24 g.) was hydrogenated at atmospheric pressure over pre-reduced palladium–calcium carbonate (5%), no solvent being used, until 1200 ml. of hydrogen had been absorbed at 16° and 758 mm. (Calc. for semi-hydrogenation: 1275 ml.). Ether and Filtercel were added, and the catalyst was filtered off. Distillation gave cis-*n-hex-4-en-1-ol* (4·6 g., 75%), b. p. 156—160°, of which the bulk had b. p. 158—159° on redistillation, n_D^{20} 1·4420 (Found: C, 72·5; H, 11·7. $C_6H_{12}O$ requires C, 71·9; H, 12·1%). The 1-*naphthylurethane* crystallised as long needles [from light petroleum (b. p. 40—60°)], m. p. 74—75° (Found: C, 75·95; H, 6·8; N, 5·55%), which on admixture with the *trans*- 1-naphthylurethane softened at 63° and melted unsharply at 65—68°. The 4-*diphenylylurethane* crystallised as needles [from light petroleum (b. p. 80—100°)], m. p. 77·5° (Found: C, 77·55; H, 6·85%), which on admixture with the *trans*-4-diphenylylurethane had m. p. 75—77°.

3-*Chloro*-2-*ethyltetrahydropyran* [with J. H. BROOKMAN].—A series of experiments was carried out under comparable conditions to discover the effect of varying the ratio of Grignard reagent to 2 : 3-dichlorotetrahydropyran. Following the procedure for the lower homologue, 2 : 3-dichlorotetrahydropyran [prepared by chlorination of dihydropyran (84 g., 1·0 mol.) in ether (200 ml.)] was added to ethylmagnesium bromide (1·5—0·9 mol.) in the appropriate volume of ether. Discoloration and resin formation were mitigated by dropping the ethereal 2 : 3-dichlorotetrahydropyran into the middle of the well-stirred (Hershberg wire stirrer) Grignard solution. By working up as previously described, the products were distilled to give the following fractions of the *cis*- and *trans*-3-chloro-2-ethyltetrahydropyrans (forerunns and residues are omitted) :

Ethylmagnesium bromide.	B. p.	n_D^{20}.	Wt., g.	Yield, %.
1·5 mols.	53—63°/11 mm.	1·4499	34	23
	63—72°/11 mm.	1·4608	37	25
	72—81°/12 mm.	1·4638	19	13
	Total		90	61
1·3 mols.	*ca.* 50—67°/14 mm.	1·4514	26	16
	67—74°/14 mm.	1·4588	36	24
	74—82°/14 mm.	1·4653	19	13
	Total		81	53
1·1 mols.	*ca.* 50—65°/13 mm.	1·4474	23	15
	65—73°/13 mm.	1·4607	36	24
	73—81°/13 mm.	1·4651	19	13
	Total		78	52
0·9 mol.	49—65°/14 mm.	1·4563	27	19
	65—74°/14 mm.	1·4674	35	23
	74—82°/14 mm.	1·4801	(17)	—
	Total		62	42

The top fraction of the last run evidently contained unchanged 2 : 3-dichlorotetrahydropyran (Paul, *Compt. rend.*, 1944, **218**, 122, records b. p. 89—90°/20 mm., n_D^{15} 1·4957), and was dark brown (the top fractions of the other runs were only yellow to pale brown and did not contain resin). On storage of this fraction colourless needles separated, being presumably di-3-chloropyran-2-yl ether (*cf.* Paul, *loc. cit.*) formed by hydrolysis of the 2 : 3-dichlorotetrahydropyran. Riobé (*Ann. Chim.*, 1949, **4**, 593) obtained a 70% yield of the mixed *cis*- and *trans*-3-chloro-2-ethyltetrahydropyrans using 1·5 mols. ethylmagnesium bromide, and recorded for the *trans*-isomer, b. p. 69°/22 mm., n_D^{20} 1·4559, and for the *cis*-isomer, b. p. 84°/22 mm., n_D^{20} 1·4651. The presence of *cis*- and *trans*-isomers in our preparations is evident.

trans-n-*Hept*-4-*en*-1-*ol*.—Ring scission of the mixed *cis*- and *trans*-3-chloro-2-ethyltetrahydropyrans, by the procedure used for the lower homologue, gave *trans*-n-hept-4-en-1-ol, b. p. 74—76°/11 mm., n_D^{20} 1·4439. Riobé (*loc. cit.*) recorded b. p. 81·5°/17 mm., n_D^{20} 1·4442.

3-*Chloro*-2-n-*propyltetrahydropyran*.—By the procedure used for the lower homologues, 2 : 3-dichlorotetrahydropyran [prepared by chlorination of dihydropyran (210 g., 1·0 mol.) in ether (500 ml.)] was added to the Grignard reagent prepared from n-propyl bromide (370 g., 1·2 mols.) and magnesium (73 g.) in dry ether (750 ml.). Towards the end of the addition the ice-bath was allowed to melt and the ether refluxed gently. When 80 ml. of the ethereal 2 : 3-dichlorotetrahydropyran had still to be added, solid began to separate and stirring became difficult, but the addition was completed. After being worked up as previously described, the product was distilled through a Dufton column. After elimination of a forerun, b. p. 60—82°/16 mm., the mixed *cis*- and *trans*-3-chloro-2-n-propyltetrahydropyrans (249 g., 62%) were collected, b. p. 82—89°/16 mm., mainly at 85—87°, n_D^{20} 1·4588. Riobé (*loc. cit.*) obtained a 60% yield using 1·5 mols. of n-propyl bromide and recorded for the *trans*-isomer, b. p. 88°/23 mm., n_D^{20} 1·4577, and for the *cis*-isomer, b. p. 101°/23 mm., n_D^{20} 1·4659. Our product appears to consist largely of the *trans*-form.

trans-n-*Oct*-4-*en*-1-*ol*.—Ring scission of the largely *trans*-3-chloro-2-n-propyltetrahydropyran (245 g.), using powdered sodium (77 g.), and following the procedure for the lower homologues, gave *trans*-n-oct-4-en-1-ol (170 g., 88%), b. p. 86—88°/11 mm., n_D^{20} 1·4456. Another preparation [with J. H. Brookman] had b. p. 104—106·5°/30 mm., n_D^{20} 1·4451. Riobé (*loc. cit.*) recorded b. p. 95°/17 mm., n_D^{20} 1·4462.

3-*Chloro*-2-n-*butyltetrahydropyran* [with J. H. BROOKMAN].—By the procedure used for the lower homologues, 2 : 3-dichlorotetrahydropyran [prepared by chlorination of dihydropyran (252 g., 1·0 mol.) in ether (600 ml.)] was added to the Grignard reagent prepared from n-butyl bromide (452 g., 1·1 mols.) and magnesium (61 g.) in dry ether (550 ml.). Before all the ethereal 2 : 3-dichlorotetrahydropyran could be added the reaction mixture set solid and the addition was discontinued. The unused solution corresponded to 21 g. of dihydropyran, showing that 1·2 mols. of n-butylmagnesium bromide had been used. After working up as previously described, the product was distilled, and after elimination of a forerun the mixed *cis*- and *trans*-3-chloro-2-n-butyltetrahydropyrans (303 g., 63%) were collected in three fractions : b. p. 83—90°/11 mm., n_D^{20} 1·4532 (32 g.); b. p. 90—103°/11 mm., n_D^{20} 1·4618 (264 g.); and b. p. 103—108°/11 mm., n_D^{20} 1·4670 (6 g.). Riobé (*loc. cit.*) obtained a 73% yield of mixed *cis*- and *trans*-isomers using 1·5 mols. of n-butylmagnesium bromide and recorded for the *trans*-isomer, b. p. 101°/21 mm., n_D^{20} 1·4571, and for the *cis*-isomer, b. p. 114°/21 mm., n_D^{20} 1·4659. Our lower and upper fractions, therefore, are substantially pure *trans*- and *cis*-forms respectively.

trans-n-Non-4-en-1-ol [with J. H. BROOKMAN].—Ring scission of the mixed *cis-* and *trans*-3-chloro-2-*n*-butyltetrahydropyrans (270 g.), as above, with powdered sodium (75 g.), gave *trans*-*n*-non-4-en-1-ol (183 g., 84%), b. p. 101—105°/13 mm., n_D^{20} 1·4476. Riobé (*loc. cit.*) recorded a 90% yield of this alcohol having b. p. 108·5°/17 mm. and n_D^{20} 1·4494.

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347. *Stereochemical Studies of Olefinic Compounds. Part III. Ring Scission of 3-Halogeno-2-alkyltetrahydrofurans as a Route to Alk-3-en-1-ols of Known Configuration and as a Method of Chain Extension by Four Methylene Groups.*

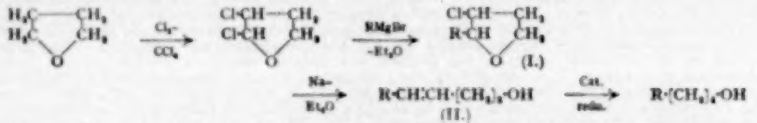
By LESLIE CROMBIE and STANLEY H. HARPER.

The preparation and ring scission of 3-chloro-2-alkyltetrahydrofurans is investigated as a route to alk-3-en-1-ols and thence, by catalytic reduction, as a method of chain extension by four methylene groups.

Interaction of 2 : 3-dichlorotetrahydrofuran with methylmagnesium bromide gives *cis-* and *trans*-3-chloro-2-methyltetrahydrofuran, separable by distillation. Although ring scission, with sodium, of the *trans*-isomer gives *trans*-n-pent-3-en-1-ol containing not more than a trace of the *cis*-alcohol, the *cis*-isomer gives a mixture of *cis-* and *trans*-n-pent-3-en-1-ol, containing a substantial proportion of the *cis*-alcohol. The scission of *cis-* and *trans*-3-chloro-2-ethyltetrahydrofuran to *n*-hex-3-en-1-ol gives similar results. Assignments of configurations of the alcohols are based on comparison with authentic specimens of the *cis-* and *trans*-alcohols (Part I), through their infra-red absorption and mixed melting points of derivatives. In confirmation the alcohols derived from the *cis*-3-chloro-2-alkyltetrahydrofurans are converted, by carboxylation of the Grignard reagents derived from the bromides, into *n*-hex- and *n*-hept-4-enoic acids respectively. Crystallisation of the *p*-bromophenacyl esters gives in each case the known *cis-* and *trans*-derivatives.

In contrast to the ring scission of 3-chloro-2-alkyltetrahydropyrans (Part II), scission of the mixed *cis-* and *trans*-3-chloro-2-alkyltetrahydrofurans, for the cases we have examined, does not lead to alk-3-en-1-ols of a single configuration. Mechanisms for these ring scissions are discussed.

In Part II (preceding paper) we described the preparation of 2-1′-halogenoalkyltetrahydrofurans and of *cis-* and *trans*-3-chloro-2-alkyltetrahydropyrans and the investigation of their ring scission by sodium with particular reference to the stereochemistry of the alk-4-en-1-ols formed. In this paper we describe a similar investigation of the preparation and ring scission of *cis-* and *trans*-3-chloro-2-alkyltetrahydrofurans (I) as a route to alk-3-en-1-ols (II). No 3-chloro-2-alkyltetrahydrofurans had been described when this study was started, so the following scheme was examined :



2 : 3-Dichlorotetrahydrofuran had been prepared by the chlorination of tetrahydrofuran in carbon tetrachloride at 0°, under anhydrous conditions (Reppe and Kröper, to I. G. Farbenind. A.-G., G.P. 703,956, 1941). Normant (*Compt. rend.*, 1948, **226**, 185) has since claimed yields of up to 90%, though Stoll and Commarmont (*Helv. Chim. Acta*, 1949, **32**, 597) obtained only 34%. We find that chlorination at 30—35° gives consistent yields of 70%. Addition of 2 : 3-dichlorotetrahydrofuran (1 mol.) in ether to the alkylmagnesium bromide (1·5 mols.) gave the 3-chloro-2-alkyltetrahydrofuran (I; R = Me and Et) in good yield. Each of these products was separated by fractional distillation into two isomers boiling some 15° apart, which differed appreciably in physical properties (Table I) and gave different infra-red absorption spectra. On the assumption that the Auwers–Skita generalisations are applicable to tetrahydrofurans, we assign the *cis*-configuration to the higher-boiling isomers and the *trans*-configuration to the lower-boiling. At this stage Normant (*Compt. rend.*, 1948, **226**, 733) briefly reported a similar investigation, but gave only single boiling points for his 3-chloro-2-alkyltetrahydrofurans. Subsequently he stated (*L'Ind. Parfumerie*, 1948, **3**, 138) that his products had a spread of boiling point and were probably *cis-trans*-mixtures. Fractional distillation of the precursory 2 : 3-dichlorotetrahydro-

furan gave no indication of heterogeneity, so that either the *cis*- and *trans*-isomers have similar boiling points or the substitution gives substantially one isomer.

Ring scission with sodium of the mixed *cis*- and *trans*-3-chloro-2-methyltetrahydrofurans gave a pentenol similar to that recorded by Normant (Table II). It was shown to be α-pent-3-en-1-ol (II; R = Me) by catalytic reduction to α-amyl alcohol and by the isolation of acetaldehyde as the sole volatile aldehyde on ozonisation. However, when this (α + β)-α-pent-3-en-1-ol was converted into the bromide and the derived Grignard reagent carboxylated, the α-hex-4-enoic acid [a] so obtained gave a heterogeneous *p*-toluidide and *p*-bromophenacyl ester. Similarly (α + β)-α-hex-3-en-1-ol (II; R = Et) (Table III) obtained on ring scission of the mixed *cis*- and *trans*-3-chloro-2-ethyltetrahydrofurans yielded a α-hept-4-enoic acid giving heterogeneous derivatives. In contrast therefore to the ring scission of *cis*- and *trans*-3-chloro-2-alkyltetrahydropyrans, in which both isomers yield the *trans*-α-alk-4-en-1-ol, scission of the mixed *cis*- and *trans*-3-chloro-2-methyl(and -ethyl)tetrahydrofurans gives both *cis*- and *trans*-α-pent(and hex)-3-en-1-ol.

TABLE I.

3-Chloro-2-alkyltetrahydrofuran.	B. p.	d_4^{20}.	n_D^{20}.	$[R_L]_D$ Found.	$[R_L]_D$ Calc.
trans-2-Methyl-	130°	1·087	1·4420	29·36	29·60
cis-2-Methyl-	145	1·098	1·4520	29·38	29·60
trans-2-Ethyl-	150	1·058	1·4463	33·95	34·22
cis-2-Ethyl-	165	1·078	1·4553	33·90	34·22

TABLE II.

α-Pent-3-en-1-ol.	B. p.	n_D^{20}.	1-Naphthylurethane, m. p.	*p*-Nitrophenyl urethane, m. p.	Ref.
(α + β)-	137—138°	1·4356	—	—	1
	137—138	—	—	—	2
α-	136—137	1·4343	92°	77°	1
β-	137—138	1·4355	74—76	71	1
cis-	139—141	1·4386	88—89	76	3
trans-	136—137	1·4340	93	80	3

Corresponding α-hex-4-enoic acid.	M. p.	B. p.	n_D^{20}.	*p*-Bromophenacyl ester, m. p.	Ref.
(α + β)-	—	117—119°/24 mm.	1·4380	—	1
α-	− 1° to + 1°	102—103°/13 mm.	1·4388	82·0—82·5°	1
β-	−17° to −15	98°/11 mm.	1·4396	{54·0—55·5 {81·0—82·5	1
cis-	−35° to −34	106°/14 mm.	1·4403	55	4
trans-	− 1° to + 1	108—109°/19 mm.	1·4387	82·5	4

[1] Crombie and Harper, this paper. [2] Normant, *Compt. rend.*, 1948, **226**, 733. [3] Crombie and Harper, Part I, *J.*, 1950, 873. [4] Crombie and Harper, *J.*, 1950, 1152.

TABLE III.

α-Hex-3-en-1-ol.	B. p.	n_D^{20}.	1-Naphthylurethane, m. p.	3 : 5-Dinitrobenzoate, m. p.	*p*-Nitrophenylurethane, m. p.	4-Diphenylylurethane, m. p.	Ref.
(α + β)-	67—71°/19 mm.	1·4377	—	—	—	—	1
(α + β)-	60°/12 mm.	—	—	—	—	—	2
(α + β)-	58—60°/12 mm.	1·4398	—	20—22°	—	—	3
α-	63—64°/16 mm.	1·4385	68—69°	46—47·5	84—85°	99·5°	1
β-	63—64°/15 mm.	1·4395	60·0—60·5	27—29	76—79	73—77	1
cis-	66—67°/19 mm.	1·4384	69—70	49	72·5—73·5	91·0—91·5	4
trans-	52—53°/9 mm.	1·4374	69—70	47—48	84—85	101	4

Corresponding α-hept-4-enoic acids.	B. p.	n_D^{20}.	*p*-Bromophenacyl ester, m. p.	Ref.
(α + β)-	123—125°/20 mm.	1·4407	—	1
β-	114—115°/13 mm.	1·4416	47°, 78—79°	1
cis-	115—116°/12 mm.	1·4403	46	5
trans-	104—105°/7 mm.	1·4398	78—79	5

[1] Crombie and Harper, this paper. [2] Normant, *Compt. rend.*, 1948, **226**, 733. [3] Stoll and Commarmont, *Helv. Chim. Acta*, 1949, **32**, 597. [4] Crombie and Harper, Part I, *J.*, 1950, 873. [5] Crombie and Harper, forthcoming publication.

The separated *trans*- and *cis*-3-chloro-2-methyltetrahydrofurans were each subjected to ring scission, to give α- and β-α-pent-3-en-1-ol respectively (Table II), while *trans*- and *cis*-3-chloro-2-

[a] Geneva numbering.

ethyltetrahydrofuran similarly gave α- and β-*n*-hex-3-en-1-ol (Table III). Although the 1-naphthylurethanes of the α- and β-alcohols had different melting points, when admixed there was no appreciable depression. The infra-red absorption spectra of α- and β-*n*-hex-3-en-1-ol (Figs. 1 and 2) show a similar location of the main bands, each has a strong band at 9·55 μ. (primary

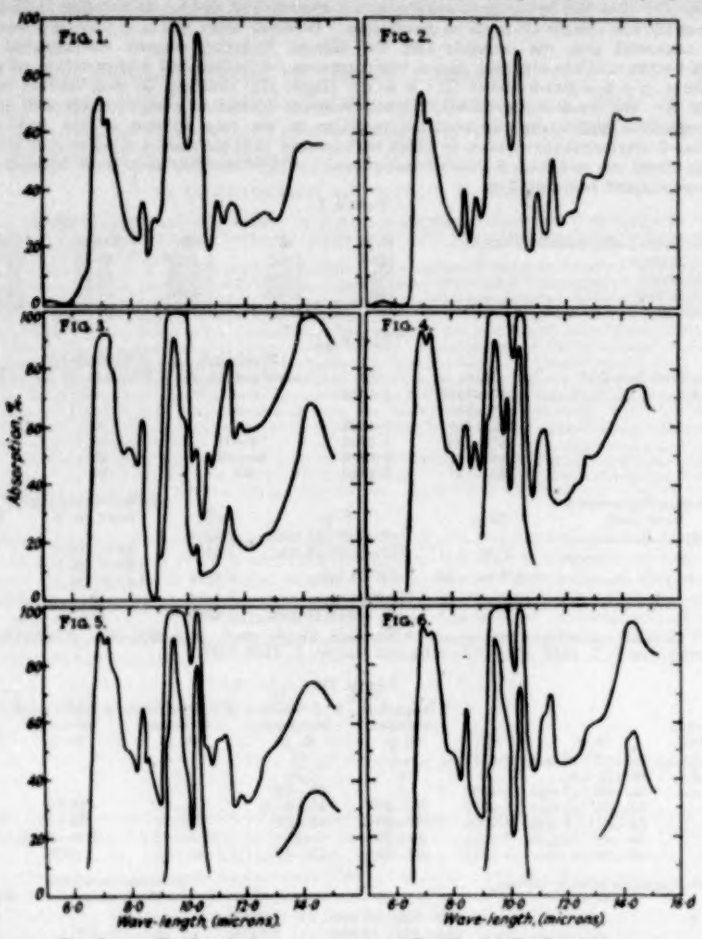


Fig. 1.—α-n-*Hex*-3-*en*-1-*ol*.
Fig. 2.—β-n-*Hex*-3-*en*-1-*ol*.
Fig. 3.—cis-n-*Pent*-3-*en*-1-*ol*.
Fig. 4.—trans-n-*Pent*-3-*en*-1-*ol*.
Fig. 5.—α-n-*Pent*-3-*en*-1-*ol*.
Fig. 6.—β-n-*Pent*-3-*en*-1-*ol*.

hydroxyl), but the intensity of the band at 10·3 μ. ("*trans*") is lower in the case of the β-alcohol. Comparison of the spectrum of α-*n*-hex-3-en-1-ol with that of authentic *trans*-*n*-hex-3-en-1-ol (Crombie and Harper, Part I, *J.*, 1950, 873; Fig. 2) suggested identity of the alcohols, which was confirmed by the absence of melting-point depression on admixture of the 1-naphthylurethanes and the 3 : 5-dinitrobenzoates. The spectrum of β-*n*-hex-3-en-1-ol is consistent with

this alcohol being a mixture of *cis*- and *trans*-*n*-hex-3-en-1-ol, since it shows both the "*trans*" band at 10·3 μ. and the band at 11·5 μ. which is present strongly in the spectrum of the pure *cis*-isomer (*loc. cit.*, Fig. 1). In addition, the increase in intensity at 13·9 μ. and minor details of the spectrum are consistent with the presence of a substantial proportion of the *cis*-isomer. Attempts to resolve the 1-naphthylurethane of β-*n*-hex-3-en-1-ol by crystallisation were unsuccessful. The alcohol was therefore converted, *via* the bromide, into a *n*-hept-4-enoic acid (Table III) and the *p*-bromophenacyl ester fractionally crystallised. Two isomeric esters were isolated, the less soluble being identical with *p*-bromophenacyl *trans*-*n*-hept-4-enoate, prepared from authentic *trans*-*n*-pent-2-en-1-ol, and the more soluble with the ester prepared from authentic *cis*-*n*-hex-3-en-1-ol. β-*n*-Hex-3-en-1-ol is therefore rigidly established as a mixture of commensurate proportions of *cis*- and *trans*-*n*-hex-3-en-1-ol.

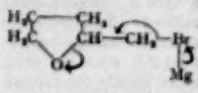
The α- and β-n-pent-3-en-1-ols exhibited analogous properties. That the α-form is substantially *trans*-*n*-pent-3-en-1-ol was shown by the identity of its 1-naphthylurethane with authentic *trans*-*n*-pent-3-en-1-yl 1-naphthylurethane (Part I, *loc. cit*). Conversion of the β-form into a *n*-hex-4-enoic acid (Table II) and fractional crystallisation of the *p*-bromophenacyl ester gave *p*-bromophenacyl *cis*- and *trans*-*n*-hex-4-enoates, identical with authentic specimens (Crombie and Harper, *J.*, 1950, 1152; therein described as hex-3-enoic acid, according to the nomenclature then used in the *Journal*). For comparison the infra-red absorption spectra of the pure *cis*- and *trans*-*n*-pent-3-en-1-ols, prepared by us (Part I, *loc. cit.*), have now been determined (Figs. 3 and 4). The spectrum of the *trans*-isomer shows the characteristic strong band at 10·3 μ., whilst the *cis*-isomer possesses a very weak band at this wave-length, but a new band at 11·5 μ. Furthermore the intensity at 14—15 μ. is greater in the case of the *cis*-isomer. These features parallel those already described for the *trans*- and *cis*-*n*-hex-3-en-1-ols. The spectrum of α-*n*-pent-3-en-1-ol (Fig. 5) is generally similar to that of the *trans*-isomer and is, in accordance with the chemical evidence, quite dissimilar from that of the *cis*-isomer. There are, however, signs that α-*n*-pent-3-en-1-ol contains a trace of the *cis*-isomer for the trough at 8·8 μ. and the pip at 11·3 μ. may be due to this cause. It is possible that this is due to the difficulty of achieving a sharp separation of the precursory *cis*- and *trans*-3-chloro-2-methyltetrahydrofurans. The β-alcohol is clearly a mixture of *cis*- and *trans*-*n*-pent-3-en-1-ols, for the spectrum (Fig. 6) contains the characteristic features of both isomers; this again accords with the chemical evidence. Thus the ring scission of mixed *cis*- and *trans*-3-chloro-2-alkyltetrahydrofurans, for the cases examined here, is unsuitable for the extension of carbon chains by the stereochemically homogeneous unit, $\cdot CH_2CH{:}CH{\cdot}[CH_2]_3{\cdot}OH$, but is suitable for extension by the unit, $\cdot[CH_2]_4{\cdot}OH$, after catalytic hydrogenation.

Stoll and Commarmont (*loc. cit.*) have recently repeated the ring scission described by Normant on what, from the evidence given here, was a mixture of *cis*- and *trans*-3-chloro-2-ethyltetrahydrofuran. They converted the alcoholic product into a 3 : 5-dinitrobenzoate (m. p. 20—22°), which after repeated crystallisation gave a small amount of pure derivative (m. p. 46·5—48°). This was not identical with *cis*-*n*-hex-3-enyl 3 : 5-dinitrobenzoate (m. p. 48°) and they suggested it was the product of a side-reaction, probably the ester of a *n*-hex-2-en-1-ol. In the light of this paper it is clearly the 3 : 5-dinitrobenzoate of *trans*-*n*-hex-3-en-1-ol, the main product of the ring scission, and we have confirmed this conclusion by a mixed melting-point determination with a specimen kindly provided by Dr. M. Stoll. In connection with Stoll and Commarmont's paper it will be apparent that our early views as to the nature of the ring scission product, recorded as a footnote to their paper, have now been revised as we had not then detected the presence of *cis*-*n*-hex-3-en-1-ol. Stoll and Commarmont's crude product, like our own (Table III), was a mixture of *cis*- and *trans*-isomers. The confusion was due to incorrect data in the literature for what had been claimed as pure *trans*-*n*-hex-3-en-1-ol; this we have since corrected (Part I, *loc. cit.*).

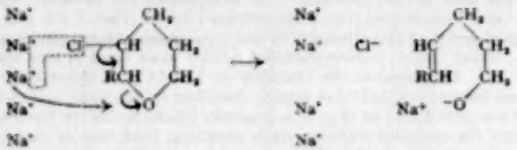
The data presented in this and the preceding paper, relating configurations of certain 3-chloro-2-alkyltetrahydropyrans, 3-chloro-2-alkyltetrahydrofurans, and 2-1′-bromoalkyltetrahydrofurans to those of the ethylenic alcohols formed on ring scission, permit a preliminary discussion of the mechanism of this reaction.

Three earlier suggestions have been made as to the course of similar fissions. Paul (*Bull. Soc. chim.*, 1933, [iv], **53**, 421) considered the ring scission of tetrahydrofurfuryl bromide by magnesium to proceed through an intervening Grignard reagent; but Robinson and Smith (*J.*, 1936, 195) and more recently Amstutz (*J. Org. Chem.*, 1944, **9**, 310) have clearly shown that a Grignard reagent is not formed. Paul subsequently (*Bull. Soc. chim.*, 1935, [v], **2**, 745) suggested the intervention of the sodium "alkyl" when using sodium, but by analogy this is improbable. Although we invariably observe a blue to purple colour during these ring scissions with sodium,

similar to those observed during the Wurtz reaction, which might be attributed to the intervention of a sodium alkyl, the colour is probably due to the inclusion of sodium atoms in the sodium chloride crystal lattice (cf. Fritz Ephraim, "Inorganic Chemistry," 5th Edn., Gurney and Jackson, p. 247). Robinson and Smith (*loc. cit.*) represented the ring scission of tetrahydrofurfuryl bromide by magnesium as proceeding from the metal acting as an electron donor to the bromine, thereby inducing electron recession through the β- and the α-carbon atom to break the α-carbon–oxygen bond—essentially a heterolytic process as illustrated. In contrast Amstutz (*loc. cit.*) postulated homolytic fission of the carbon–halogen bond to yield a free radical ($R{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}$) which then undergoes either Wurtz coupling or fission at the β-carbon–oxygen bond. We regard a free radical mechanism for the ring scission by sodium as improbable. Certainly the ethylenic alcohol is formed to the extent of ~90%, so that any other reactions proceed to a very minor extent.



Reaction must proceed at the surface of the metallic sodium where, on the approach of a suitably orientated molecule, we suggest ring scission is initiated by nucleophilic attack on the halogen of the surface electrons, followed by electron recession to the α-carbon atom and thereafter fission of the α-carbon–oxygen bond with concomitant release of two sodium ions, *e.g.*:



As regards ring scission of the 3-chloro-2-alkyltetrahydropyrans, examination of models shows that, if the reaction proceeds by a "normal" bimolecular mechanism (S_N2 with reference to the α-carbon atom) through the duplet of electrons liberated by the breaking of the carbon–chlorine bond attacking the α-carbon atom on the opposite side to that at which the α-carbon–oxygen bond simultaneously breaks (*i.e.*, "inversion" of the α-carbon atom), then *trans*-3-chloro-2-alkyltetrahydropyrans would give *trans*-α-alk-4-en-1-ols, whilst the *cis*-pyrans would give *cis*-alcohols. In contrast, if after separation of the chlorine the α-carbon–oxygen bond also breaks, leaving the α-carbon atom as a carbonium ion (S_N1 with respect to the α-carbon atom), then ethylenic-bond formation can occur without inversion at the α-carbon atom. This type of substitution is generally accompanied by "racemisation" of the α-carbon atom owing to the formation of a planar carbonium ion. Steric or other factors, however, may cause subsequent union in one of the two possible ways to be inhibited, with the result that somewhat more than 50% of one of the isomers is produced. Repulsion of the alkyl side-chain from the sodium surface might facilitate union with retention of configuration. By this scheme *trans*-pyrans would give both *cis*- and *trans*-α-alk-4-en-1-ols, with the former predominating, whilst *cis*-pyrans would give mixtures with the *trans*-isomer greatly predominating, for the repulsion of the alkyl group would be greater in the case of the *cis*-pyrans owing to its closer proximity to the chlorine and hence to the sodium surface. We have shown, certainly for methyl and most probably for ethyl, α-propyl, and α-butyl, that both *trans*- and *cis*-3-chloro-2-alkyltetrahydropyran give solely the *trans*-α-alk-4-en-1-ol. The ring scissions of the *trans*- and *cis*-pyrans must therefore proceed by different mechanisms, the incidence of an S_N1 mechanism being caused by the steric suppression of the more "normal" S_N2 reaction by the change of geometric configuration. For *trans*-pyran to give solely *trans*-alcohol the scission must proceed by the S_N2 mechanism, whereas, for *cis*-pyran to give *trans*-alcohol with no more than a trace of *cis*-alcohol, scission must proceed by the S_N1 mechanism with substantially complete retention of configuration. As this change of mechanism to S_N1 with nearly complete retention of configuration occurs for the smallest possible alkyl group (methyl) it appears that a bimolecular scission of a *cis*-pyran cannot be realised, *i.e.*, *cis*-α-alk-4-en-1-ols are not accessible by the direct ring scission of 3-chloro-2-alkyltetrahydropyrans.

Next, with regard to the 3-chloro-2-alkyltetrahydrofurans, where we have shown that, for methyl and ethyl, the *trans*-furan gives *trans*-α-alk-3-en-1-ol, it is clear that the ring scission parallels that of the *trans*-pyrans in proceeding by a S_N2 mechanism. However, as we have shown, the *cis*-furans give mixtures of *cis*- and *trans*-alcohols, in which the latter predominate. This is capable of two explanations: either the ring scission proceeds mainly by the S_N1

mechanism without inversion, to give *trans*-alcohol, and partly by the S_N2 mechanism to give *cis*-alcohol; or the ring scission proceeds only by the S_N1 mechanism but with substantial inversion leading to both *trans*- and *cis*-alcohols. The latter appears preferable, particularly as the S_N2 mechanism clearly does not participate in the presumably analogous scission of the *cis*-pyrans. This change must be connected with the differing geometry of the two systems, where in comparison with the presumably puckered and flexible six-membered tetrahydropyran ring, the five-membered tetrahydrofuran ring is both rigid and substantially planar. Further their geometry requires that in the *cis*-furans the alkyl group will be slightly farther from the chlorine than in the *cis*-pyrans. This will reduce the hindering effect of the alkyl group to the approach of the chlorine atom to the sodium surface and also the tendency of the α-carbon atom to react with retention of configuration; *i.e.*, substantial "racemisation" will occur leading to the observed results. If this view is correct, increasing the steric effect of the alkyl group should lead to stronger repulsion from the sodium surface and hence to greater union without inversion; *i.e.*, by suitable variation of the alkyl group it should be possible to suppress the formation of *cis*-alcohol and to obtain solely *trans*-α-alk-3-en-1-ol from the ring scission of both *cis*- and *trans*-3-chloro-2-alkyltetrahydrofurans. This possibility will be investigated.

The single case of the ring scission of a 2-1′-halogenoalkyltetrahydrofuran, where alkyl is methyl, that we have examined appears at first sight to parallel the ring scission of *cis*-3-chloro-2-methyl(or -ethyl)tetrahydrofuran in giving a mixture of *trans*- and *cis*-α-alk-4-en-1-ol, in which the former predominates. The problem is however more complex. The bromide presumably consists of two racemic pairs of diastereoisomers, which incidentally may account for its observed spread of boiling point, and these correspond to the *trans*- and *cis*-furans. Their varying modes of ring scission, by S_N2 and S_N1 mechanisms, will parallel those discussed above but will lead to *trans*–*cis*-mixtures of alk-4-en-1-ols of varying composition. However a detailed analysis is too speculative in view of the limited experimental data.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. The infra-red absorption spectra were determined by Miss I. M. Friedmann, to whom we are indebted, with a Grubb Parsons spectrometer using the pure liquids in cells of 20—50-μ. thickness.

2 : 3-*Dichlorotetrahydrofuran*.—Commercial tetrahydrofuran, containing a phenolic antioxidant, was distilled from sodium wire, and the portion, b. p. 66—67°, used immediately. Chlorine, from a cylinder, dried by passage through concentrated sulphuric acid, was passed into a solution of the distilled tetrahydrofuran (216 g.) in dry carbon tetrachloride (200 ml.) containing iodine (1 g.). Chlorination was started at 25° and within a few minutes the brown colour disappeared and the temperature rose to 30—35°, at which it was kept by cooling in running water. An efficient reflux condenser was necessary on the exit side of the all-glass apparatus to prevent loss of the volatile tetrahydrofuran. Evolution of hydrogen chloride was evident after 4 hours and chlorination was continued until reaction ceased (24—30 hours), as shown by a fall in temperature and passage of unreacted chlorine. Dry nitrogen was then bubbled through the solution to remove most of the dissolved chlorine and hydrogen chloride. The carbon tetrachloride was removed through a column under partly reduced pressure and the residue distilled through a 40-cm. Dufton column, to give **2 : 3**-dichlorotetrahydrofuran (300 g., 71%), b. p. 65·5—70°/23 mm., which was sufficiently pure for preparative purposes. On redistillation the bulk (275 g.) had b. p. 63—66°/21 mm., n_D^{20} 1·4841 (Found : C, 34·9; H, 4·7; Cl, 49·2. Calc. for $C_4H_6OCl_2$: C, 34·1; H, 4·3; Cl, 50·3%). In our initial experiments at 0°, we found that sunlight was necessary for the reaction to start. On one occasion the chlorine merely dissolved until the flask was removed from the ice-bath, reaction then beginning suddenly with some violence. Most batches of **2 : 3**-dichlorotetrahydrofuran assumed a red colour when kept which was not removed by redistillation.

3-*Chloro*-2-*methyltetrahydrofuran*.—**2 : 3**-Dichlorotetrahydrofuran (260 g., 1·0 mol.) was dropped slowly into a well stirred (Hershberg wire stirrer) ice-cold Grignard reagent prepared from methyl bromide vapour and magnesium turnings (67·5 g., 1·5 g.-atoms) in anhydrous ether (600 ml.). After storage at room temperature, usually overnight, the excess of Grignard reagent was decomposed by the careful addition of cold ammonium chloride solution, with stirring and external cooling. The ethereal layer was separated and the aqueous layer just acidified with concentrated hydrochloric acid and further extracted with ether. The extracts were bulked, washed, and dried (Na_2SO_4—K_2CO_3). Distillation gave mixed *cis*- and *trans*-3-chloro-2-methyltetrahydrofurans (177 g., 82%), b. p. 40—50°/19 mm., n_D^{20} 1·4487. This mixture was fractionated through a 50 × 1·5-cm. helices-packed column with variable take-off and electrically heated jacket, at atmospheric pressure, to give the lower-boiling trans- (Found : C, 49·8; H, 7·6; Cl, 29·6. C_5H_9OCl requires C, 49·8; H, 7·5; Cl, 29·4%) and cis-**3-*chloro*-2-*methyltetrahydrofuran*** (Found : C, 49·8; H, 7·6; Cl, 29·6%) (see Table 1).

3-*Chloro*-2-*ethyltetrahydrofuran*.—By the procedure used for the lower homologue **2 : 3**-dichlorotetrahydrofuran (68 g., 1·0 mol.) was treated with the Grignard reagent prepared from ethyl bromide (79 g., 1·5 mols.) and magnesium (17·6 g.) in dry ether (300 ml.), to give the mixed *cis*- and *trans*-3-chloro-2-ethyltetrahydrofuran (56·5 g., 85%), b. p. 60—72°/21 mm., n_D^{20} 1·4510. This mixture was fractionally distilled to give quite readily the higher-boiling **cis-3-*chloro*-2-*ethyltetrahydrofuran*** (b. p. 165°) (Found : C, 53·3; H, 8·5; Cl, 26·3. $C_6H_{11}OCl$ requires C, 53·55; H, 8·2; Cl, 26·3%), but the b. p. of the **trans-3-*chloro*-2-*ethyltetrahydrofuran*** (Found : C, 53·4; H, 8·4; Cl, 25·7%) was rather wide (150—155°) and the purity of this isomer was judged by the refractive indices and densities of successive fractions. The

physical properties of these isomers are recorded in Table I. The *trans*-3-chloro-2-methyl(and -ethyl)-tetrahydrofurans had the pleasanter odours and were stable to light, whereas the *cis*-isomers became yellow in a few hours and eventually deep brown.

Ring Scission of 3-Chloro-2-methyltetrahydrofuran.—The same procedure was used as that for the ring scission of 3-chloro-2-methyltetrahydropyran (p. 1712). In this way the mixed *cis*- and *trans*-3-chloro-2-methyltetrahydrofuran (160 g.) gave (α + β)-n-pent-3-en-1-ol (97 g., 83%), b. p. 137—138°, n_D^{20} 1·4356. The yield was between 80 and 90% in three other preparations.

Ring scission of separated *trans*-3-chloro-2-methyltetrahydrofuran (31·7 g.) similarly yielded α-n-pent-3-en-1-ol (13·1 g., 57%), b. p. 136—137°, n_D^{20} 1·4343 (Found: C, 69·0; H, 11·9. Calc. for $C_5H_{10}O$: C, 69·7; H, 11·7%). This alcohol (130 mg.) was heated with 1-naphthyl isocyanate (243 mg.) in a sealed tube at 100° for 30 minutes. The contents of the tube were extracted with light petroleum (b. p. 60—80°), and a small quantity of dinaphthylurea was filtered off. The 1-naphthylurethane (240 mg.) separated from the filtrate in needles, m. p. 86—88°, which 3 further crystallisations raised to 92° (Found: C, 75·5; H, 6·6; N, 5·2. Calc. for $C_{16}H_{17}O_2N$: C, 75·3; H, 6·7; N, 5·5%). This m. p. was not depressed (92—93°) on admixture with the 1-naphthylurethane of authentic *trans*-α-pent-3-en-1-ol (p. 877). By a similar procedure α-n-pent-3-en-1-ol (84 mg.) and *p*-nitrophenyl isocyanate (164 mg.) gave the *p-nitrophenylurethane* (200 mg.) as needles which after two crystallisations from light petroleum (b. p. 80—90°; 3 parts by vol.)–carbon tetrachloride (1 part) had m. p. 77° (Found: N, 10·7. $C_{12}H_{14}O_4N_2$ requires N, 11·2%). This m. p. was not depressed on admixture with the *p*-nitrophenylurethane of *trans*-α-pent-3-en-1-ol (below), but was depressed to 70·5—73° on admixture with the derivative of *cis*-α-pent-3-en-1-ol (below). These procedures for the preparation of urethanes were also used in the earlier Parts of this series.

Ring scission of *cis*-3-chloro-2-methyltetrahydrofuran (33 g.) proceeded more vigorously than that of the *trans*-isomer, to give β-n-pent-3-en-1-ol (17·1 g., 71%), b. p. 136—137°, n_D^{20} 1·4355 (Found: C, 70·2; H, 11·2%). This alcohol (130 mg.) treated as above gave the 1-naphthylurethane (250 mg.) as felted needles, m. p. 74—76°, which was unchanged after 2 further crystallisations (Found: C, 74·6; H, 6·7; N, 5·5%). A 1 : 1 mixture with the "α" 1-naphthylurethane softened at 75° and cleared at 85°. The *p*-nitrophenylurethane (180 mg. from 84 mg. of alcohol) crystallised as needles, m. p. 71°, which was not raised by recrystallisation (Found: N, 10·7%). A 1 : 1 mixture with the "α" *p*-nitrophenylurethane had m. p. 70—73°.

trans-α-Pent-3-en-1-ol (p. 877) has been further characterised by the preparation of the *p-nitrophenylurethane*, which after purification by treatment with charcoal and crystallisation from a mixture of light petroleum (b. p. 40—60°) and carbon tetrachloride was obtained as small colourless crystals, m. p. 80° (Found: C, 57·3; H, 5·75; N, 11·5. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·65; N, 11·2%). *cis*-α-Pent-3-en-1-ol (p. 877) has similarly been further characterised by preparation of the *p-nitrophenylurethane*, m. p. 76° (Found: C, 57·1; H, 5·55; N, 11·4%). A mixture of these two derivatives melted unsharply at 71—73°.

Both α- and β-n-pent-3-en-1-ol were recovered unisomerised after being heated with a crystal of iodine in a sealed tube at 100° for 8 hours: the α-alcohol so treated gave a 1-naphthylurethane, m. p. 86—87°, and the β-alcohol gave a 1-naphthylurethane, m. p. 74°.

Ozonisation of α- and β-n-Pent-3-en-1-ol.—The calculated volume of ozonised oxygen was passed through (α + β)-n-pent-3-en-1-ol (500 mg.) in carbon tetrachloride (15 ml.) cooled in ice. Water (20 ml.) was then added and the volatile aldehyde swept into a solution of dimedon in water by a slow stream of nitrogen during 24 hours. The dimedon derivative of acetaldehyde (420 mg.) separated, having m. p. 139°, which recrystallised from aqueous ethanol as needles or plates, m. p. 140·5°, and did not depress the m. p. of an authentic specimen (m. p. 140—141°).

Ozonisation of α- and β-n-pent-3-en-1-ol separately gave similar results. Thus the dimedon derivative (100 mg.) of the volatile aldehyde from the α-alcohol (170 mg.) had m. p. 140—141°, with softening at 138°, without crystallisation. One recrystallisation gave m. p. 141° and when admixed with authentic acetaldehyde dimedon derivative this derivative had m. p. 141·0—141·5°. The β-alcohol (300 mg.) gave on ozonolysis 240 mg. of dimedon derivative, m. p. 139—142°. One crystallisation from ethanol raised this to m. p. 141—142° (a 1 : 1 mixture with an authentic sample had m. p. 141—142°).

Hydrogenation of α- and β-n-Pent-3-en-1-ol.—(α + β)-n-Pent-3-en-1-ol (163 mg.) was hydrogenated at atmospheric pressure in ethyl acetate (10 ml.), using pre-reduced palladium–barium sulphate (100 mg.; 5% Pd). Hydrogen (40·5 ml. at N.T.P.) was absorbed in 20 minutes (calc.: 43·0 ml.), whereafter absorption stopped. Filtercel was then added and the catalyst filtered off. The ethyl acetate was carefully distilled off and the residual alcohol converted into its 3 : 5-dinitrobenzoate, m. p. 43—44°, not depressed on admixture with authentic n-amyl 3 : 5-dinitrobenzoate, m. p. 46—47° (43—45°).

α-n-Pent-3-en-1-ol (194 mg.) absorbed hydrogen (48·0 ml. at N.T.P.) during 20 minutes (calc.: 50·5 ml.), and the 3 : 5-dinitrobenzoate of the reduction production had m. p. 43·0—43·5°. The β-alcohol (245 mg.) absorbed hydrogen (63·0 ml. at N.T.P.) (Calc.: 64 ml.) and the saturated product gave a 3 : 5-dinitrobenzoate, m. p. 42·5—44·0°. On admixture with authentic n-amyl 3 : 5-dinitrobenzoate neither of the above m. p.s were depressed.

α- and β-n-Pentyl-3-enyl Bromides.—Phosphorus tribromide (140 g.) was added during 3 hours to a stirred mixture of (α + β)-n-pent-3-en-1-ol (112 g.) and pyridine (30 g.), cooled in ice. After a further 2 hours at room temperature the crude bromide was distilled out by direct heating of the flask until the orange residue frothed up. The crude bromide was diluted with light petroleum (b. p. 40—60°), to aid separation, and washed twice with 10% hydrochloric acid, then 10% sodium hydroxide, and water. After drying (Na_2SO_4) and removal of the light petroleum the residue was twice distilled under partly reduced pressure, to give (α + β)-n-pent-3-enyl bromide (142 g.), b. p. 89—97°/225 mm., n_D^{20} 1·4700.

α-n-Pent-3-enyl bromide prepared from the α-alcohol had b. p. 90—94·5°/260 mm., n_D^{20} 1·4690, while the β-bromide prepared from the β-alcohol had b. p. 95—98°/280 mm., n_D^{20} 1·4670.

α- and β-n-Hex-4-enoic Acids.—Magnesium turnings (25·5 g.) were covered with anhydrous ether (60 ml.) and reaction started by the addition of a few ml. of (α + β)-n-pent-3-enyl bromide. Further

ether (200 ml.) was then added and the remainder of the bromide (120 g. in all) dropped in during 3 hours. After a further hour the reaction mixture was cooled in alcohol–solid carbon dioxide, and carbon dioxide, dried by concentrated sulphuric acid, was passed in with stirring. When the mass became pasty and difficult to stir, a large excess of powdered solid carbon dioxide was added and the mixture stirred by hand and left for 2 hours. The product was decomposed by ice-cold 25% sulphuric acid, and the ethereal layer separated. The aqueous phase was thoroughly extracted with ether, and the bulked ethereal extracts were washed with water. The ethereal solution was then extracted with 50-ml. portions of 10% sodium hydroxide solution, until a test portion gave no turbidity on acidification. The alkaline extracts were covered at 0° with a layer of light petroleum (b. p. 40—60°), and 25% sulphuric acid was added with stirring until the aqueous phase was just acid to Congo-red. Separation of the light petroleum layer, washing, drying, and removal of the solvent gave (α + β)-*n*-hex-4-enoic acid, which when distilled had b. p. 117—119°/24 mm. and n_D^{20} 1·4380 (64·5 g., 65%). The *p*-toluidide and the *p*-bromophenacyl ester of this acid were heterogeneous and melted over a range.

In like manner α-*n*-pent-3-enyl bromide (4·1 g.) was converted into α-*n*-hex-4-enoic acid (2·1 g., 67%), m. p. −1° to +1°, b. p. 102·5—103·0°/13 mm., n_D^{20} 1·4388 (Found: equiv., 114·1. Calc. for $C_6H_{10}O_2$: equiv., 114·1). Letch and Linstead (*J.*, 1934, 1994) record m. p. +1°, b. p. 102°/12 mm., n_D^{20} 1·4367, for a specimen of *n*-hex-4-enoic acid, which from its mode of preparation must have the *trans*-configuration (cf. Crombie and Harper, p. 1152; therein named as hex-3-enoic acid). The *p*-bromophenacyl ester of the α-acid formed colourless needles, m. p. 82·0—82·5°, unchanged on admixture with authentic *trans*-ester (Crombie and Harper, *loc. cit.*) (m. p. 81·5—82·5°).

Similarly β-*n*-pent-3-enyl bromide (2·8 g.) was converted into β-*n*-hex-4-enoic acid (0·95 g., 45%), m. p. −17° to −15°, b. p. 98°/11 mm., n_D^{20} 1·4396 (equiv., 115·7). The *p*-bromophenacyl ester was clearly heterogeneous and was therefore crystallised from aqueous ethanol. The less soluble fractions were collected and crystallised 3 times from ethanol, giving light colourless needles, m. p. 81·0—82·5°, which failed to depress the m. p. of authentic *trans*-ester on admixture (mixed m. p. 82·0—82·5°). The more soluble fraction, isolated by dilution of the mother-liquors with water, melted at 49—53°, after softening. Recrystallisation from ethanol–water gave a product, as colourless plates, m. p. 56°, which when admixed with authentic *p*-bromophenacyl *cis*-*n*-hex-4-enoate (colourless plates, m. p. 55°) (Crombie and Harper, *loc. cit.*) had m. p. 54—55·5°.

Ring Scission of 3-Chloro-2-ethyltetrahydrofuran.—By the procedure described above the mixed *cis*- and *trans*-3-chloro-2-ethyltetrahydrofuran (81 g.) were converted into (α + β)-*n*-hex-3-en-1-ol (49 g., 81%), b. p. 67—71°/19 mm., n_D^{20} 1·4377.

Ring scission of *trans*-3-chloro-2-ethyltetrahydrofuran (15·3 g.) was slow in starting and proceeded much less vigorously than that of the *cis*-isomer, to give α-*n*-hex-3-en-1-ol (7·4 g., 53%), b. p. 63—64°/16 mm., n_D^{20} 1·4385 (Found: C, 72·0; H, 12·2. Calc. for $C_6H_{12}O$: C, 71·9; H, 12·1%). This alcohol was characterised by the 1-naphthylurethane, which formed glistening flat needles, m. p. 68—69° (after 2 crystallisations) depressed on admixture with *cis*-*n*-hex-3-en-1-yl 1-naphthylurethane (m. p. 71°) (p. 876) to 59—60°, but not (68—70°) on admixture with *trans*-*n*-hex-3-en-1-yl 1-naphthylurethane (m. p. 69—70°) (*loc. cit.*).

α-*n*-Hex-3-en-1-ol (500 mg.) and 3 : 5-dinitrobenzoyl chloride (1·2 g.) in benzene containing pyridine gave the crude ester (1·05 g.). One crystallisation from light petroleum (b. p. 40—60°) gave a sample, m. p. 38·5—40·5°, which by repeated crystallisation was raised to 46·0—47·5°. Admixture of this with authentic *cis*-*n*-hex-3-enyl 3 : 5-dinitrobenzoate (m. p. 49°) (*loc. cit.*) gave a depression of the m. p. to 34°, but admixture with authentic *trans*-ester (m. p. 47°) (*loc. cit.*) gave no depression. The *p*-nitrophenylurethane, m. p. 84—85°, and the 4-diphenylylurethane, m. p. 99·5°, of *trans*-*n*-hex-3-en-1-ol described previously (*loc. cit.*) were prepared from this alcohol, made by ring scission of *trans*-3-chloro-2-ethyltetrahydrofuran. When either of these derivatives was mixed with the corresponding derivative of *cis*-*n*-hex-3-en-1-ol (*loc. cit.*) depressions of the m. p. was observed. We have now prepared the *p*-nitrophenylurethane and 4-diphenylylurethane of *trans*-*n*-hex-3-en-1-ol, made by reduction of *n*-hex-3-yn-1-ol (kindly provided by Dr. F. Sondheimer; cf. this vol., p. 861) with sodium in liquid ammonia. These derivatives had m. p. 84—85° and m. p. 101° respectively after recrystallisation and are cited in Table III.

Ring scission of *cis*-3-chloro-2-ethyltetrahydrofuran (21 g.) by the above method proceeded vigorously, to yield β-*n*-hex-3-en-1-ol (13·5 g., 86%), b. p. 63—64°/15 mm., n_D^{20} 1·4395 (Found: C, 72·5; H, 12·3%). The heterogeneity of the β-alcohol was demonstrated by preparation of the 1-naphthylurethane, which crystallised from light petroleum (b. p. 40—60°) as glistening needles, m. p. 59°, raised by two further crystallisations only to m. p. 60·0—60·5° (Found: C, 75·9; H, 6·6; N, 5·3. Calc. for $C_{17}H_{19}O_2N$: C, 75·8; H, 7·1; N, 5·2%). The 3 : 5-dinitrobenzoate separated as an oil, which eventually solidified and, crystallised as needles from light petroleum (b. p. 40—60°) (cooling to −80°), had m. p. 28°. The *p*-nitrophenylurethane and 4-diphenylylurethane likewise melted over a range, 76—79° and 73—77° respectively.

α- and β-n-Hex-3-enyl Bromides.—(α + β)-*n*-Hex-3-en-1-ol (46 g.) and pyridine (10 g.) were treated with phosphorus tribromide (50 g.), following the procedure used for the lower homologue, to give (α + β)-*n*-hex-3-enyl bromide (53 g., 71%), b. p. 47—53°/15 mm., n_D^{20} 1·4690.

β-*n*-Hex-3-enyl bromide prepared from β-*n*-hex-3-en-1-ol had b. p. 81—83°/77 mm., n_D^{20} 1·4708.

α- and β-n-Hept-4-enoic Acids.—(α + β)-*n*-Hex-3-enyl bromide (50 g.) was converted into the Grignard reagent with magnesium (9·0 g.) in anhydrous ether (120 ml.) and carboxylated by the procedure described for the lower homologue. The resulting (α + β)-*n*-hept-4-enoic acid (26·6 g., 68%) had b. p. 123—125°/20 mm., n_D^{20} 1·4407 (Found: equiv., 127·7. Calc. for $C_7H_{12}O_2$: equiv., 128·2).

In like manner β-*n*-hex-3-enyl bromide was converted into β-*n*-hept-4-enoic acid, b. p. 114—115·5°/14 mm., n_D^{20} 1·4416 (Found: equiv., 128·7). The *p*-bromophenacyl ester was clearly heterogeneous and when crystallised from aqueous ethanol was easily resolved into two esters. The more soluble ester, when recrystallised from ethanol, had m. p. 47°, and did not depress the m. p. of authentic *cis*-ester (m. p. 46·5°). As first isolated, the less soluble ester melted poorly at about 68°, but 2 crystallisations from ethanol raised this m. p. to 78—79°. On admixture with authentic *p*-bromophenacyl

trans-α-hept-4-enate (m. p. 78—79°) the mixture had m. p. 78—79°. The preparation of these two reference esters will be described in a forthcoming part of this series.

We are indebted to Dr. G. H. Williams for helpful discussions of the mechanism of ring scission. We gratefully acknowledge grants from the Agricultural Research Council, the Central Research Fund of the University of London, the Royal Society, and the Chemical Society which have defrayed the expenses of the investigation described in this and the preceding paper.

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348. *The Preparation of Benziminazoles and Benzoxazoles from Schiff's Bases. Part II.*

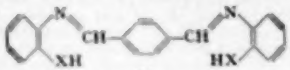
By F. F. STEPHENS and J. D. BOWER.

The method described in Part I has been extended, principally to the synthesis of *Bz*-substituted benzoxazoles. New reagents are described for this reaction, and a mechanism is postulated.

In Part I (*J.*, 1949, 2971) the preparation of 2-phenyl-benziminazoles and -benzoxazoles, by dehydrogenation of their corresponding Schiff's bases with lead tetra-acetate, was described. With one exception, the compounds described therein were without substituents in the *Bz*-ring. In order to examine the generality of the method and to prepare compounds of potential medicinal or chemotherapeutic interest (to be reported later, see however B.P. Appln. 8,680/49) the synthesis of *Bz*-substituted benziminazoles and benzoxazoles was attempted.

In a few cases, when aromatic aldehydes were condensed with substituted *o*-phenylenediamines, stable, highly coloured, recrystallisable compounds were formed. These were assumed to be Schiff's bases and were dehydrogenated by lead tetra-acetate in the normal manner. In other cases, the condensation products were converted into benziminazoles merely by being heated or on recrystallisation. Thus, *p*-nitrobenzaldehyde reacts with *N*-methyl-*o*-phenylenediamine (in 50% acetic acid) to give a bright red solid which on recrystallisation (from ethanol or pyridine) is converted into 2-*p*-nitrophenyl-1-methylbenziminazole. This compound is identical with that prepared by Wiedenhagen and Train (*Ber.*, 1942, **75**, 1936) by cupric acetate oxidation of the mixed aldehyde and amine. Again, 3 : 4-diaminobenzonitrile and *p*-cyanobenzaldehyde react in boiling glacial acetic acid to give a pale yellow solid (m. p. *ca.* 300°) which is unaffected by lead tetra-acetate. If the components react in ethanol, an orange-red solid is obtained which if heated slowly also melts at *ca.* 300°, but if heated rapidly melts at *ca.* 180°. On boiling the red solid with acetic acid or recrystallising it from benzonitrile, it becomes identical with the pale yellow one [5(6)-cyano-2-*p*-cyanophenylbenziminazole]. In this type of reaction Elderfeld *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 44) have supplied spectroscopic evidence that the initial product is a benziminazoline and have suggested that this spontaneously oxidises to a benziminazole. [Cf. also the work on the condensation of aldehydes with *o*-amino-thiophenols by Lankelma and Sharnoff (*J. Amer. Chem. Soc.*, 1931, **53**, 2654).] In view of these results, little work was done on the preparation of *Bz*-substituted benziminazoles.

Condensation of aldehydes with substituted *o*-amino-phenols gave stable Schiff's bases (soluble in dilute alkali) in all the cases examined and ring-closure by heat or recrystallisation was never observed. From these Schiff's bases 2-phenylbenzoxazoles containing a variety of substituents in the *Bz*-ring, *e.g.*, chloro, bromo, nitro, dinitro, cyano, carbomethoxy, methyl, and sulphamyl, were prepared by the method described in Part I (*loc. cit.*). The Schiff's base (I; X = O), terephthalidenebis-*o*-aminophenol, was converted into *p*-phenylenebis-2-benzoxazole (II; X = O) and, in addition, two heterocyclic groups (pyridyl and furyl) and the trichloromethyl group (from chloral) were inserted in the 2-position of benzoxazole.



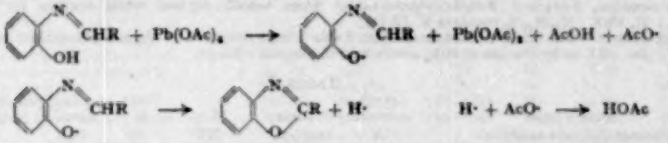
(I.)

(II.)

Terephthalidenebis-*o*-phenylenediamine (I; X = NH) was prepared and, although oxidation proceeded normally, the product could not be purified. *p*-Phenylenebis-2-1-methylbenziminazole (II; X = NMe) was prepared.

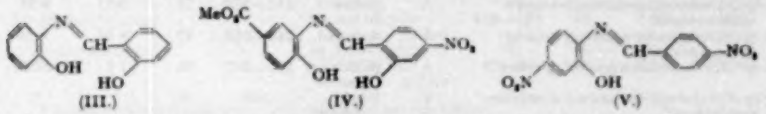
The preparation of 2-*p*-nitrophenylbenzoxazole from its Schiff's base was attempted by means of a number of other reagents. These included cupric acetate, persulphates, periodic acid, mercuric acetate, sodium bismuthate (cf. Rigby, *Nature*, 1949, **164**, 185), benzoquinone, chloranil, *N*-bromosuccinimide, and benzoyl peroxide. From the action of the first named, the Schiff's base was recovered quantitatively and unchanged. No benzoxazole was isolated from the reaction with persulphate or periodic acid. The other reagents all gave the desired product, chloranil, *N*-bromosuccinimide, and benzoyl peroxide being particularly active (see Experimental); the yields from mercuric acetate and sodium bismuthate were very small. Desai, Hunter, and Khalidi (*J.*, 1934, 1186) unsuccessfully attempted this ring-closure by means of hydrogen peroxide and potassium ferricyanide.

Considering the preparation of benzoxazoles (where stable Schiff's bases are precursors), it is probable that ring closure by lead tetra-acetate proceeds by a free-radical mechanism, the stages of which may be represented as follows:



Some evidence for these views is supplied by the following: (*a*) reagents found to cause easy ring closure are known to generate free radicals, (*b*) when 4-nitro-2-*p*-nitrobenzylideneaminotoluene reacted in boiling acetic acid with lead tetra-acetate the Schiff's base was quantitatively recovered, (*c*) the first step in the above scheme has been postulated by Cosgrove and Waters (*J.*, 1949, 3189) in the reaction of phenols with benzoyl peroxide, (*d*) the yields obtained in the *simple* cases (cf. Part I, *loc. cit.*) appear to be unrelated to the electronic character of the substituent in the 2-phenyl ring (cf. the recent work on the Pschorr reaction by Hey and Osbond, *J.*, 1949, 3172), (*e*) parallel work (in collaboration with D. G. Wibberley; to be reported later) has shown that the azo-methine linkage may be replaced by the ethylene bond (leading to coumarones). From these considerations it was deduced that sulphuryl chloride, reacting with the liberation of chlorine atoms, would effect ring closure. This was found to be the case (see Experimental).

If the idea of primary attack on the hydroxy-group is accepted, this will explain the low yield obtained in the preparation of 2-*o*-hydroxyphenylbenzoxazole where the Schiff's base (III) has two hydroxy-groups exposed, and attack on only one can lead to the desired cyclisation. In this respect, and again revealing the effects of substituents, a good yield was obtained in the



(III.) (IV.) (V.)

oxidation of (IV) whereas (V) was extremely resistant to attack by lead tetra-acetate. Finally, if the benzoxazoles contained halogen in the 6-position, they appeared to be prepared with especial ease.

The intermediates required in this work were mostly prepared by established methods. 3 : 4-Diaminobenzonitrile has been prepared by Bogert and Wise (*J. Amer. Chem. Soc.*, 1910, **32**, 1494) and by Borsche *et al.* (*Ber.*, 1916, **49**, 2233), but no yields are given. Catalytic reduction of 3-nitro-4-aminobenzonitrile was found satisfactory for this preparation, and the route described in the experimental section more convenient than those employed by the above workers.

Experimental.

(All m. p.s were determined with Anschütz thermometers.) (See also B.P. Applns. 2478/49 and 8680/49.)

p-Acetamidobenzaldoxime.—Hydroxylamine hydrochloride (10 g.), dissolved in a mixture of pyridine (45 ml.) and ethanol (50 ml.), was added to a solution of *p*-acetamidobenzaldehyde (20 g.) in pyridine (100 ml.) and ethanol (25 ml.). The mixture was refluxed for 40 minutes, the solvents removed by vacuum distillation on the steam-bath, and water (250 ml.) added to the residual oil to cause complete

precipitation of the product. Filtration and recrystallisation of this from water gave *p*-acetamidobenzaldoxime (19 g.; m. p. 210°) (Found: N, 15·7. Calc. for $C_9H_{10}O_2N_2$: N, 15·7%).

p-Acetamidobenzonitrile.—*p*-Acetamidobenzaldoxime (160 g.) was refluxed (30 minutes) with acetic anhydride (400 ml.), the mixture was cooled, diluted with water (3000 ml.) and neutralised with 50% sodium hydroxide solution. Filtration followed by recrystallisation (from water) gave *p*-acetamidobenzonitrile (87 g.; m. p. 206·5°) (Found: N, 17·3. Calc. for $C_9H_8ON_2$: N, 17·5%).

3-Nitro-4-aminobenzonitrile.—*p*-Acetamidobenzonitrile (50 g.) was added during 1 hour to a mixture of sulphuric acid (300 ml.; *d* 1·84) and potassium nitrate (67 g.) maintained below 0°. The mixture was kept at 0° for 2 hours, and then poured on ice, and the crude 3-nitro-4-acetamidobenzonitrile removed by filtration. Hydrolysis by refluxing sulphuric acid (30 ml.; *d* 1·84) and water (270 ml.) for 30 minutes, followed by two recrystallisations from water, gave 3-nitro-4-aminobenzonitrile (40 g.; m. p. 163°) (Found: N, 25·4. Calc. for $C_7H_5O_2N_3$: N, 25·7%).

3 : 4-Diaminobenzonitrile.—A suspension of 3-nitro-4-aminobenzonitrile (5 g.) in ethanol (120 ml.) was hydrogenated at room temperature in the presence of Adams's catalyst (initial hydrogen pressure: 50 lbs. per sq. in.). Reduction was complete within 15 minutes, after which the product was isolated by evaporation of the solvent. Recrystallisation from water gave 3 : 4-diaminobenzonitrile (3·5 g.; m. p. 146°) as white needles becoming pink in the air (Found: N, 31·7. Calc. for $C_7H_7N_3$: N, 31·6%). The quinoxaline, *6-cyano-2 : 3-diphenylquinoxaline* (from benzil), formed white needles, m. p. 184° (Found: N, 13·8. $C_{21}H_{13}N_3$ requires N, 13·7%).

Schiff's Bases.—The Schiff's bases, detailed in Table I, were prepared by the general method described in Part I (*loc. cit.*), or by the use of 50% acetic acid in place of ethanol.

TABLE I.

Schiff's base.	Crystn. solvent.	Colour.	M. p.	Yield, %.	Analysis, N%, found.	required.
N-p'-Nitrobenzylidene-4-methyl-o-phenylenediamine	A	maroon	137°	64	16·7	16·5
N-p'-Acetamidobenzylidene-4-methoxy-o-phenylenediamine	A	greenish-yellow	174	70	15·1	14·8
Terephthalidenebis-o-phenylenediamine	F	orange	212—214	95	17·9	17·8
5-Chloro-2-(p-cyanobenzylideneamino)-phenol	C	yellow	202—204	82	[1]	[1]
4-Nitro-2-benzylideneaminophenol [2]	A	yellow	195	82	11·85	11·6
4-Nitro-2-(p-nitrobenzylideneamino)-phenol	A	yellow	239—240	88	14·8	14·6
4-Nitro-2-(p-acetamidobenzylideneamino)-phenol	E	yellow	249—250	98	13·8	14·0
5-Nitro-2-(p-nitrobenzylideneamino)-phenol	E	brown	261—263	90	14·7	14·6
5-Nitro-2-(p-cyanobenzylideneamino)-phenol	E	yellow	236—237	98	15·7	15·7
4 : 6-Dinitro-2-(p-nitrobenzylideneamino)-phenol	E	pale yellow	228—229	80	16·7	16·9
2-(p-Nitrobenzylideneamino)-4-cyano-phenol	A	deep yellow	232—233	90	15·7	15·7
2-(p-Cyanobenzylideneamino)-4-cyano-phenol	aq. C	biscuit	216	68	16·5	17·0
2-(p-Nitrobenzylideneamino)-4-carbomethoxyphenol	A	yellow	211—212	71	9·17	9·33
2-(p-Nitrosalicylideneamino)-4-carbomethoxyphenol	A	deep red	248—249	82	8·69	8·86
3-(p'-Nitrobenzylideneamino)-p-cresol	A	golden yellow	202—203	82	11·1	10·9
2-(p-Nitrobenzylideneamino)-4-sulphonamidophenol	E	bright yellow	256	90	[3]	[3]
2-(p-Acetamidobenzylideneamino)-4-carbomethoxyphenol	D	biscuit	232—233	65	9·08	8·97
2-(p-Acetamidobenzylideneamino)-4-sulphonamidophenol	aq. C	pale yellow	193	90	[4]	[4]
Terephthalidenebis-*o*-aminophenol	B	yellow	220—221 [5]	95	[6]	[6]

Crystallisation solvents used were: A = ethanol, B = *n*-butanol, C = glacial acetic acid, D = dioxan, E = benzonitrile, and F = pyridine.

[1] Found: N, 10·3; Cl, 13·5. $C_{14}H_9ON_3Cl$ requires N, 10·9; Cl, 13·8%. [2] Raiford and Linak (*J. Amer. Chem. Soc.*, 1945, **67**, 878). [3] Found: N, 13·0; S, 9·87. $C_{13}H_{11}O_3N_3S$ requires N, 13·1; S, 9·97%. [4] Found: N, 12·5; S, 9·47. $C_{14}H_{13}O_4N_3S$ requires N, 12·6; S, 9·61%. [5] Levi (*Gazzetta*, 1929, **59**, 544) claims m. p. 213°. [6] Found: C, 76·8; H, 4·7; N, 9·06. Calc. for $C_{20}H_{14}O_2N_2$: C, 76·0; H, 5·06; N, 8·86%.

Benziminazoles and *Benzoxazoles.*—Unless otherwise stated, the benziminazoles and benzoxazoles, detailed in Table II, were obtained by the general method described in Part I (*loc. cit.*).

2-p-Nitrophenylbenzoxazole by Means of Other Reagents.—(*a*) *Chloranil.* 2-(*p*-Nitrobenzylideneamino)-phenol (1 g.) and chloranil (1 g.) were boiled under reflux in xylene (30 ml.) for 3 hours. The hot solution was filtered and, on cooling, 2-*p*-nitrophenylbenzoxazole (0·72 g.), m. p. 268°, was obtained.

(*b*) *Benzoyl peroxide.* The above Schiff's base (1 g.) and benzoyl peroxide (1 g.) were heated under

reflux in chloroform (50 ml.) for 90 minutes. Evaporation of the solvent followed by removal of benzoic acid (dilute alkali) gave a crude product which, after recrystallisation (from xylene), gave 2-*p*-nitrophenylbenzoxazole (0·5 g.), m. p. 288°.

TABLE II.

Compound.	Crystn. solvent.	Colour.	M. p.	Yield, %.	Analysis, N %. found.	required.
Benziminazoles.						
5(6)-*Cyano*-2-p-*nitrophenyl* [1]	PhCN	yellow	348°	56 *	20·9	21·2
5(6)-*Cyano*-2-p-*cyanophenyl* [1]	$PhNO_2$	pale yellow	346—347	41 *	23·3	22·9
2-p-*Nitrophenyl*-5(6)-*methyl*	aq. EtOH	orange	205	88	16·3	16·6
2-*p*-Nitrophenyl-1-methyl [1] [2]	EtOH	pale yellow	214	47 *	[3]	[3]
p-*Phenylenebis*-2-1-*methylbenziminazole* †	dioxan	white	288—289	25	16·4	16·6
Benzoxazoles.						
6-*Chloro*-2-p-*cyanophenyl*	AcOH	white	194—195	95	[4]	[4]
6-*Chloro*-2-p-*chlorophenyl*	EtOH	white	148—149	61 *	[5]	[5]
6-*Bromo*-2-p-*cyanophenyl* †	AcOH	pink	215	98	9·31	9·37
5-*Nitro*-2-*phenyl*	EtOH	cream	172	90	11·7	11·7
5-*Nitro*-2-p-*nitrophenyl*	PhCN	buff	257—258	70	14·6	14·7
5-*Nitro*-2-p-*acetamidophenyl*	dioxan	pale yellow	259—260	85	14·3	14·1
6-*Nitro*-2-p-*nitrophenyl* [6]	PhCN	pale yellow	221	10	14·4	14·7
6-*Nitro*-2-p-*cyanophenyl*	AcOH	yellow	205	60	15·6	15·8
5 : 7-*Dinitro*-2-p-*nitrophenyl*	nitro-methane	pale yellow	208—209	80	17·1	17·0
5-*Cyano*-2-p-*nitrophenyl*	AcOH	yellow	296—298	55	15·7	15·8
5-*Cyano*-2-p-*cyanophenyl*	xylene	white	277—278	70	[7]	[7]
5-*Carbomethoxy*-2-p-*nitrophenyl*	AcOH	pink	198—199	80	9·24	9·40
5-*Carbomethoxy*-2-(2-*hydroxy*-4-*nitrophenyl*)	dioxan	yellow	242—243	85	[8]	[8]
5-*Carbomethoxy*-2-(p-*acetamidophenyl*) [9]	AcOH	salmon pink	274	95	9·06	9·03
5-*Carbomethoxy*-2-2′-*pyridyl*	n-BuOH	buff	168—169	80	10·9	11·0
5-*Methyl*-2-p-*nitrophenyl*	EtOH	pale yellow	209	90	11·2	11·0
5-*Sulphonamido*-2-p-*nitrophenyl*	AcOH	pale yellow	254—255	90	[10]	[10]
5-*Sulphonamido*-2-p-*acetamidophenyl* [11]	$PhNO_2$	pink	327—329	86	[11]	[11]
5-*Sulphonamido*-2-2′-*pyridyl*	water	brown	[12]	86	15·6	15·3
p-*Phenylenebis*-2′-*benzoxazole*	ethyl benzoate	yellow	354	84	[13]	[13]
2-o-Hydroxyphenyl	aq. AcOH	pale yellow	123—124	26	6·63	6·63
2-*Trichloromethyl* [14]	aq. EtOH	white [15]	57	60	[17]	[17]
2-Furyl	aq. EtOH	pale yellow	82—84	70	7·76	7·57

* Schiff's base not isolated; yield calculated on the amine.

† Schiff's base not purified.

[1] Dehydrogenation occurs on recrystallisation or on heating the precursor. [2] *Methochloride*, white plates (from water), m. p. 253° (Found: C, 58·6; H, 5·4; N, 13·1; Cl, 11·6. $C_{16}H_{14}O_2N_2Cl$ requires C, 59·3; H, 4·6; N, 13·8; Cl, 11·7%). [3] Found: C, 66·3; H, 4·18. Calc. for $C_{14}H_{11}O_2N_3$: C, 66·4; H, 4·35%. [4] Found: Cl, 13·5. $C_{14}H_7ON_2Cl$ requires Cl, 13·9%. [5] Found: Cl, 27·0. $C_{13}H_7ONCl_2$ requires Cl, 26·9%. [6] Oxidation carried out in boiling glacial acetic acid and an excess of lead tetra-acetate employed. [7] Found: C, 74·0; H, 2·8; N, 17·4. $C_{14}H_7ON_3$ requires C, 73·5; H, 2·9; N, 17·1%. [8] Found: C, 57·9; H, 3·3; N, 9·8. $C_{15}H_{12}O_4N_2$ requires C, 57·3; H, 3·2; N, 8·9%. [9] Hydrolysis with 50% sulphuric acid gives 2-p-*aminophenylbenzoxazole*-5-*carboxylic acid* (m. p. >300° decomp.) (Found: N, 11·0. $C_{14}H_{10}O_3N_2$ requires N, 11·0%). [10] Found: N, 13·1; S, 9·7. $C_{13}H_9O_4N_3S$ requires N, 13·2; S, 10·0%. [11] Acid hydrolysis, followed by neutralisation, gave 5-*sulphonamido*-2-p-*aminophenylbenzoxazole* (m. p. 290—291°) (Found: N, 14·0; S, 10·9. $C_{19}H_{11}O_3N_3S$ requires N, 14·5; S, 11·1%); *hydrochloride* (from dilute hydrochloric acid), colourless plates (m. p. 242° decomp.) Found: N, 12·2; Cl, 10·2. $C_{19}H_{11}O_3N_3S,HCl,H_2O$ requires N, 12·2; Cl, 10·3%). [12] Found: N, 12·4; S, 9·95. $C_{19}H_{12}O_2N_4S$ requires N, 12·7; S, 9·6%. [13] Depends upon rate of heating; *ca.* 230°. [14] Found: C, 77·1; H, 4·1; N, 9·3. $C_{14}H_{13}O_2N_2$ requires C, 76·9; H, 3·85; N, 9·9%. [15] Prepared from 2-(2 : 2 : 2-*trichloroethylideneamino*)*phenol* (m. p. 101°) (Found: N, 5·9. $C_8H_4ONCl_3$ requires N, 5·9%), which was obtained by interaction of chloral and o-aminophenol in glacial acetic acid. [16] White needles becoming purple in the air. [17] Found: Cl, 44·5. $C_8H_4ONCl_3$ requires Cl, 45·0%.

(*c*) *N-Bromosuccinimide.* The Schiff's base (1 g.) and *N*-bromosuccinimide (0·83 g.) were boiled under reflux in dry carbon tetrachloride for 3 minutes. The solvent was removed and the residue washed with hot water and recrystallised twice from xylene to give pale yellow needles (0·4 g.), m. p. 268°.

(*d*) *Sulphuryl chloride.* The Schiff's base (1 g.) in benzene (30 ml.) was treated with sulphuryl chloride (0·5 ml.), and the mixture boiled under reflux for 30 minutes. The product (m. p. 261°) separated on cooling and was recrystallised from xylene. Yield 0·4 g. (m. p. 268°).

Mixed m. p.s with material prepared by lead tetra-acetate oxidation (Part I, *loc. cit.*) were carried out in each of the above cases.

We thank Dr. G. M. Dyson for his interest in this work and for permission to publish it, also Miss P. A. Page and Mr. J. V. Smart for all analyses, and Mr. J. A. Coombe for experimental assistance.

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349. *The Relative Reactivity of Aromatic Double Bonds. Part II.* Addition of Osmium Tetroxide to Substituted* 1 : 2-*Benzanthracenes.*

By G. M. BADGER and K. R. LYNN.

The effect of various *meso*-substituents on the rate of addition of osmium tetroxide to the 3 : 4-double bond of 1 : 2-benzanthracene has been investigated. Methyl, acetoxymethyl, and phenyl groups were found to facilitate the reaction, and bromo-, acetoxy-, and cyano-, substituents to retard the addition. *meso*-Methoxy-groups were found to exert little effect. The rate of addition to 5-methyl-1 : 2-8 : 9-dibenzacridine has also been studied.

9-Methoxy-1 : 2-benzanthracene has been prepared by cyclisation of *o*-2-naphthylmethylbenzoic acid to 9-acetoxy-1 : 2-benzanthracene, followed by cleavage with Grignard reagent and methylation with methyl sulphate.

THREE compounds appear to function as " double-bond " reagents: ozone, diazoacetic ester, and osmium tetroxide. These reagents readily react with ethylenic double bonds to form addition compounds, and they also attack certain aromatic double bonds. Ozone is the most vigorous reagent, even benzene and pyridine being readily, if slowly, attacked. Diazoacetic ester also reacts with benzene, with elimination of nitrogen. With polycyclic compounds, the selective addition of ozone, and of diazoacetic ester, to the more reactive double bonds only may be brought about. Under the conditions so far employed, osmium tetroxide does not attack benzene, but reacts only with aromatic bonds which have pronounced double-bond character. Unlike the usual electrophilic reagents, such as NO_2^+ and Br^+, etc., these double-bond reagents do not attack the most reactive centres in a polycyclic molecule, except in those cases in which the most reactive centres are situated at the extremities of the most reactive *bond* (Badger, *J.*, 1949, 456; Cook and Schoental, *J.*, 1948, 170; *idem*, *Nature*, 1948, **161**, 237).

The use of osmium tetroxide to determine the relative reactivity of aromatic double bonds has been described previously by one of us (Badger, *loc. cit.*; Badger and Reed, *Nature*, 1948, **161**, 238). The method has been used to study the rate of addition of osmium tetroxide to a series of cancer-producing compounds, especially the methyl derivatives of 1 : 2-benzanthracene (I). The substitution of methyl groups in this molecule was found to increase the rate of addition to the 3 : 4-bond, the magnitude of the increase being dependent on the position of substitution. It was also found that a cyano-group markedly reduced the rate of addition. A further series of compounds has now been examined, in an attempt to evaluate the effect of other substituent groups on the density of π electrons on the 3 : 4-bond. In the earlier work it was found that methyl groups exerted the maximum effect when present as *meso*-substituents. For this reason most of the compounds in the present series are *meso*-substituted benzanthracenes. The rate of addition to 5-methyl-1 : 2-8 : 9-dibenzacridine (II) has also been examined.

(I.)

(II.)

The reactions were carried out, as previously reported, in pure chloroform containing 4% pyridine at 20°. The progress of the reaction was followed by removing aliquot portions at

* *J.*, 1949, 456, is regarded as Part I of this series.

suitable intervals and estimating the colour intensity of the solution (and hence the concentration of the complex) with a Spekker absorptiometer. The rate constants for the present series of compounds are given in the accompanying table, the constants for 1 : 2-benzanthracene and its 10-methyl and 9 : 10-dimethyl derivatives being included for reference.

The earlier work showed clearly that methyl substituents facilitate the addition of osmium tetroxide, whilst the cyano-substituent definitely slows the reaction, presumably by withdrawing electrons from the double bond. The present work confirms the activating influence of the methyl group. For example, 10-acetoxy-9-methyl-1 : 2-benzanthracene reacted more rapidly than 10-acetoxy-1 : 2-benzanthracene, and 10-bromo-9-methyl-1 : 2-benzanthracene reacted more rapidly than 10-bromo-1 : 2-benzanthracene. Furthermore, 5-methyl-1 : 2-8 : 9-dibenzacridine (II) reacted with osmium tetroxide more rapidly than 1 : 2-benzanthracene. This is interesting, for the activating influence of the methyl group is offset to some extent by the deactivating influence of the heterocyclic nitrogen atom, and the addition was found to take place only slightly less rapidly than with 10-methyl-1 : 2-benzanthracene.

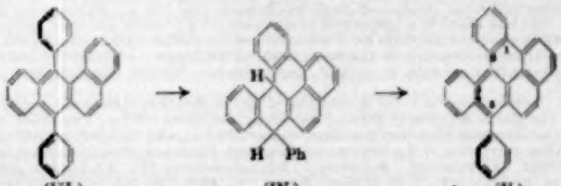
Rate of addition of osmium tetroxide to substituted 1 : 2-*benzanthracenes, in* 4% *pyridine in chloroform, at* 20°. (k_2 in g.-mol.$^{-1}$sec.$^{-1}$l.)

Compound.	$10^3\,k_2$.	Compound.	$10^3\,k_2$.
9 : 10-Dimethyl-1 : 2-benzanthracene	2·7*	9-Methoxy-1 : 2-benzanthracene	0·55
10-Methyl-1 : 2-benzanthracene	0·91*	1 : 2-Benzanthracene	0·48*
5-Methyl-1 : 2-8 : 9-dibenzacridine	0·88	9 : 10-Dimethoxy-1 : 2-benzanthracene ...	0·46
10-Bromo-9-methyl-1 : 2-benzanthracene	0·74	10-Cyano-9-methyl-1 : 2-benzanthracene	0·40*
9 : 10-Diphenyl-1 : 2-benzanthracene	0·70	10-Acetoxy-1 : 2-benzanthracene	0·34
10-Acetoxy-9-methyl-1 : 2-benzanthracene	0·62	10-Bromo-1 : 2-benzanthracene	0·27
10-Acetoxymethyl-1 : 2-benzanthracene...	0·61	9 : 10-Diacetoxy-1 : 2-benzanthracene ...	0·22

* Badger (*J.*, 1949, 456.)

The acetoxymethyl group is also activating, although less so than the methyl group, for 10-acetoxymethyl-1 : 2-benzanthracene formed the addition complex with osmium tetroxide more rapidly than 1 : 2-benzanthracene, but less rapidly than 10-methyl-1 : 2-benzanthracene. *meso*-Acetoxy- and *meso*-bromo-groups were found to retard the addition, and *meso*-methoxy-groups had little or no effect on the rate of reaction. *meso*-Phenyl groups appear to activate the 3 : 4-bond, the rate of addition to 9 : 10-diphenyl-1 : 2-benzanthracene being greater than that to unsubstituted benzanthracene.

In some respects, these results may seem surprising. For example, it is well known that in electrophilic substitutions of benzene derivatives, the methoxy-group is very strongly activating and *ortho-para* directing, whereas in the present case it seems to exert little or no effect. Moreover, the acetoxy-group is usually regarded as a weak activating group, yet it seems to act as a deactivating substituent in the present reaction. It must be remembered, however, that



(III.) (IV.) (V.)

methoxy- and acetoxy-groups have inductive and tautomeric effects which are opposite in sign, so that it is impossible to estimate, with any degree of certainty, the net effect on a reaction rate. It is known, however, that the $+T$ effect of the methoxy-group is almost wholly a polarisability effect (Bunton, Minkoff, and Reed, *J.*, 1947, 1416), and in almost all the known cases this $+T$ effect easily predominates over the $-I$ effect. The explanation for the present results may well be that in anthracene derivatives, *meso*-methoxy- and *meso*-acetoxy-groups cannot be coplanar with the ring system (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127; Spruit, *Rec. Trav. chim.*, 1949, **68**, 325). Moreover, in benzanthracene derivatives the interference with the " benz " ring is very considerable indeed. In these circumstances it is not surprising that these groups do not exert the same activating effects as in simple benzene derivatives.

On the other hand, 9 : 10-diphenyl-1 : 2-benzanthracene (III) must also be non-coplanar,

and the phenyl groups cannot be conjugated with the ring system to any marked extent. Nevertheless, *meso*-phenyl groups do increase the rate of addition of osmium tetroxide. In this connection it was thought of interest to examine the rate of addition of osmium tetroxide to 5-phenyl-1 : 2-3 : 4-dibenzpyrene (V). This compound is theoretically derived from 9 : 10-diphenyl-1 : 2-benzanthracene (III) by the loss of two hydrogen atoms. It must be admitted, however, that this conversion could not be brought about directly by heating with dehydrogenating agents. Clar's method (*Ber.*, 1930, **63**, 119), involving the isomerisation of (III) to (IV) with aluminium chloride, followed by dehydrogenation, was found to give excellent results. In 5-phenyl-1 : 2-3 : 4-dibenzpyrene, only one phenyl group is non-coplanar, and the conversion of (III) into (V) was found to cause a profound redistribution of the π electrons, for (V) reacted so slowly with osmium tetroxide that its rate could not be accurately measured by the present procedure.

It is of some interest to compare the present results with those of similar experiments on the addition of maleic anhydride, and the photo-addition of oxygen, to the *meso*-positions of anthracene derivatives. Bachmann and Kloetzel (*J. Amer. Chem. Soc.*, 1938, **60**, 481), for example, found that whilst *meso*-methyl and -ethyl groups increased the rate of addition of maleic anhydride, *meso*-phenyl groups had a retarding influence. On the other hand, Dufraisse and Bras (*Compt. rend.*, 1943, **216**, 60) found that *meso*-phenyl groups increased the rate of photo-oxidation of anthracene derivatives. *meso*-Acetoxy-groups were found to retard the addition, as was the case with the usual deactivating groups such as cyano-, carbethoxy-, and carbamyl (Dufraisse and Mathieu, *Bull. Soc. chim.*, 1947, **307**). It is also noteworthy that 9 : 10-dimethoxyanthracene was the most easily photo-oxidised compound studied by Dufraisse and Priou (*Bull. Soc. chim.*, 1939, **6**, 1649).

For the preparation of 9-methoxy-1 : 2-benzanthracene, *o*-2-naphthoylbenzoic acid was prepared from 2-bromonaphthalene by Weizmann, Bergmann, and Bergmann's method (*J.*, 1935, 1367). Reduction with activated zinc dust and dilute sodium hydroxide gave *o*-2-naphthylmethylbenzoic acid, which was cyclised by zinc chloride and acetic anhydride to *9-acetoxy-1 : 2-benzanthracene* (compare Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1937, **59**, 1028). The same acetoxybenzanthracene was also obtained, with some difficulty, by acetylation of crude 1 : 2-benz-9-anthrone prepared by reduction of 1 : 2-benzanthraquinone with aluminium powder in sulphuric acid (Cook, *J.*, 1930, 1094). The desired 9-methoxy-derivative was obtained from acetoxybenzanthracene by cleavage with *n*-butylmagnesium bromide, followed by methylation with methyl sulphate (compare Fieser and Hershberg, *loc. cit.*).

9 : 10-*Diacetoxy*-1 : 2-*benzanthracene* was obtained by reductive acetylation of 1 : 2-benzanthraquinone with zinc dust and acetic anhydride, and 9 : 10-dimethoxy-1 : 2-benzanthracene by reductive methylation (Berenblum and Schoental, *Cancer Res.*, 1943, **3**, 686).

Experimental.

o-2-*Naphthylmethylbenzoic Acid*.—*o*-2-Naphthoylbenzoic acid (10 g.) (Weizmann, Bergmann, and Bergmann, *loc. cit.*) was added to a suspension of zinc dust (15 g.) (which had been activated by contact with a 3% solution of copper sulphate for 5 minutes) and 2*N*-sodium hydroxide solution (225 c.c.), and the resulting mixture was heated on the water-bath for 18 hours. *o*-2-Naphthylmethylbenzoic acid (4·2 g.) formed colourless crystals, m. p. 135°, from toluene. Barnett and Campbell (*J.*, 1935, 1031) give m. p. 135°.

9-*Acetoxy*-1 : 2-*benzanthracene*.—(*a*) A solution of the naphthylmethylbenzoic acid (5 g.) and zinc chloride (0·4 g.) in glacial acetic acid (30 c.c.) and acetic anhydride (20 c.c.) was boiled under reflux for 1½ hours. The solution was diluted with a large volume of water, and the resulting precipitate dissolved in benzene. After extraction of the benzene solution with dilute sodium carbonate solution, and then water, the solvent was removed. 9-*Acetoxy*-1 : 2-*benzanthracene* (2·2 g.) formed almost colourless micro-prisms, m. p. 141—142°, from alcohol (Found : C, 83·9; H, 5·0. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·9%).

(*b*) The same product was obtained, in poor yield, when crude 1 : 2-benz-9-anthrone (Cook, *loc. cit.*) was boiled for 1 hour with acetic anhydride and sodium acetate.

9-*Methoxy*-1 : 2-*benzanthracene*.—9-Acetoxy-1 : 2-benzanthracene (2 g.) was added to a solution of *n*-butylmagnesium bromide (from 3·84 c.c. of *n*-butyl bromide) in anhydrous ether, and the mixture refluxed for 1 hour. Methyl sulphate (14·2 g.) in dry toluene (50 c.c.) was then added, and the mixture heated on the steam-bath, for 4 hours, allowing the ether to distil. Water was added, and the product was heated with stirring for a further hour to decompose the excess of reagent. The washed toluene layer was diluted with benzene, dried, and passed through a column of alumina to remove unchanged anthranol. Crystallisation of the residue from light petroleum gave 9-*methoxy*-1 : 2-*benzanthracene* (0·4 g.) as colourless plates, m. p. 104° (Found : C, 88·5; H, 5·6. $C_{19}H_{14}O$ requires C, 88·3; H, 5·4%). The *picrate* formed dark red-brown elongated prisms, m. p. 117—118°, from alcohol (Found : C, 61·6; H, 3·7. $C_{19}H_{14}O.C_6H_3O_7N_3$ requires C, 61·6; H, 3·5%).

9 : 10-*Diacetoxy*-1 : 2-*benzanthracene*.—A mixture of 1 : 2-benzanthraquinone (5 g.), zinc dust (20 g.), and acetic anhydride (50 c.c.) was boiled under reflux for 1 hour. After being poured into water, the

product was left to separate. Next morning, the solid was collected and extracted with alcohol and then benzene, the mixed solvent evaporated, and the product recrystallised from benzene. **9 : 10-*Diacetoxy*-1 : 2-*benzanthracene*** (4·1 g.) formed colourless needles, m. p. 217—218° (Found : C, 78·85; H, 4·5. $C_{22}H_{16}O_4$ requires C, 76·7; H, 4·7%).

9 : 10-*Dimethoxy*-1 : 2-*benzanthracene*.—A mixture of benzanthraquinone (7 g.), zinc dust (28 g.), and dilute sodium hydroxide solution was treated alternately with small portions of methyl sulphate and sodium hydroxide solution, at 100°, until the colour of the vat was completely discharged. The product (extracted from the zinc dust with alcohol) formed small colourless prisms, m. p. 136—137° (Found : C, 83·4; H, 5·5. Calc. for $C_{20}H_{16}O_2$: C, 83·3; H, 5·6%). Berenblum and Schoental (*loc. cit.*) give m. p. 137—138°. Hydrolysis of its complex with osmium tetroxide (cf. Cook and Schoental, *loc. cit.*) gave **3 : 4-*dihydroxy*-9 : 10-*dimethoxy*-3 : 4-*dihydro*-1 : 2-*benzanthracene*** as colourless needles, m. p. 184—186° (decomp.) (Found : C, 74·5; H, 5·6. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%).

Reaction Rates.—The rates of reaction were determined by the method described previously (Badger, *loc. cit.*).

We are indebted to Dr. Ng. Ph. Buu-Hoï for a gift of 5-methyl-1 : 2-8 : 9-dibenzacridine and to Mr. R. Howard for the microanalyses.

Johnson Chemical Laboratories, University of Adelaide. [*Received, February* 15*th*, 1950.]

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350. *The Mechanism of Hydrolysis of Acid Chlorides. Part I. The Effect of Hydroxyl Ions, Temperature, and Substituents on the Rate of Hydrolysis of Benzoyl Chloride.*

By R. F. Hudson and J. E. Wardill.

The velocity of hydrolysis of benzoyl chloride has been measured electrically using 50% aqueous acetone as solvent. Hydrogen-ion catalysis was not detected, in agreement with previous observations. It was found that the ratio of the bimolecular velocity constant for the reaction with hydroxyl ions to the velocity constant of the pseudo-unimolecular reaction for the neutral hydrolysis is of the same order as for the hydrolysis of benzyl chloride. In addition, the activation energies for the neutral hydrolysis of benzoyl chloride and several *p*-substituted benzoyl chlorides varied little with the nature of the substituent. This contrasts with the alcoholysis in a solvent of lower ionising power. These results have been interpreted in terms of a dual mechanism involving bimolecular substitution and unimolecular ionisation, a conclusion which is supported fully by alcoholysis studies.

Benzyl chloride is usually considered to be hydrolysed after preliminary ionisation, which is rate-determining. In support of this mechanism, it is found that substituents which increase the electron density at the reactive carbon atom increase the rate of reaction (Olivier and Berger, *Rec. Trav. chim.*, 1926, **45**, 452; 1930, **49**, 697). The effect of introducing an oxygen atom at the reactive carbon atom is to withdraw electrons from the seat of reaction, and hence to promote a bimolecular mechanism (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 613). The effect of substituents on the rate of a bimolecular reaction is less definite than for a unimolecular mechanism, owing to the relative complexity of a bimolecular transition state (see Hinshelwood, Laidler, and Timm, *J.*, 1938, 848). It is not surprising therefore that difficulty has been experienced in interpreting the experimental data in terms of this mechanism.

The hydrolyses of benzyl and benzoyl halides are similar in the following ways : (1) The rate is unaffected by the hydrogen-ion concentration, but is increased by addition of hydroxyl ions (Olivier and Berger, *Rec. Trav. chim.*, 1927, **46**, 609; Beste and Hammett, *J. Amer. Chem. Soc.*, 1940, **62**, 2481). (2) The effect of solvent in both cases is such that the rate of hydrolysis increases considerably with increasing ionising power of the solvent. (3) Benzyl halides show positive salt effects (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979). The benzoyl halides exhibit salt effects of a comparable magnitude (Peeling, Ph.D. Thesis, London, 1946).

On the other hand, the effect of substituents on the rate of hydrolysis of benzyl chloride is the reverse of the effect on the rate of the alcoholysis of benzoyl chloride. This is usually quoted as evidence of the bimolecular nature of the latter reaction. The effect of substituents on the rate of hydrolysis of benzoyl chloride differs greatly from the effect on the rate of the alcoholysis—and the former reaction cannot be interpreted simply in terms of any one mechanism.

Previous methods of following the rate of hydrolysis of benzoyl chloride were not of a high degree of accuracy, owing to the use of titration methods in relatively rapid reactions. An E.M.F. method similar to that developed by Ross and Swain (*J. Amer. Chem. Soc.*, 1946, **68**, 658) was used in the present work, and enabled activation energies to be determined and the effect of hydroxyl ions to be investigated. In addition, the original conclusion of Olivier and Berger that hydrogen ions have no effect on the rate was confirmed.

It is observed that hydroxyl ions increase the rate of hydrolysis by a bimolecular reaction superimposed on the pseudo-unimolecular solvolysis, as in the case of benzyl chloride (Beste and Hammett, *loc. cit.*). Thus the overall rate of reaction is give by the expression,

$$dx/dt = k_1(a - x) + k_2(a - x)(b - x)$$

where $(a - x)$ is the concentration of benzoyl chloride, and $(b - x)$ that of hydroxide ions at time t, k_1 the pseudo-unimolecular constant for the neutral hydrolysis, and k_2 the bimolecular constant for the reaction with hydroxyl ions.

Evaluation of k_2 for the hydrolysis of benzoyl and benzyl chlorides shows that the bimolecular reaction with hydroxyl ions affects the overall rate to approximately the same extent in the two cases, as shown by the following values:

Hydrolysis.	Medium.	D, 20°.	k_2/k_1.
(*a*) $C_6H_5{\cdot}COCl$	Water 50%, acetone 50%	51	20
(*b*) $C_6H_5{\cdot}CH_2Cl$	Water 40%, dioxan 60%	34	150

(*a*) Present work. (*b*) Beste and Hammett.

As k_1 increases greatly with increase in the dielectric constant D, it follows that the hydroxyl-ion effect is almost identical for the two substances. In some cases where the reaction is thought to be bimolecular, *e.g.*, the hydrolysis of acetic anhydride (Gold, *Trans. Faraday Soc.*, 1948, **44**, 506), the ratio is much greater, *ca.* 10^4. These results indicate that benzoyl chloride may be hydrolysed by a S_N1 mechanism in highly aqueous solvents, a possibility which is supported by the following experimental results.

Table I records the activation energies for the neutral hydrolyses of benzoyl chloride and *p*-substituted benzoyl chlorides. These values, when compared with corresponding values for the alcoholysis of triphenylmethyl and benzoyl chlorides, show that substituents in the *p*-position have little effect on E, although the rate is affected considerably (see below).

TABLE I.

	Activation energy (cals.)			
	alcoholysis			hydrolysis
p-Substituent.	triphenylmethyl chlorides.	benzoyl chlorides.		
NO_2	16,710 [a]	11,100 [a]	— [b]	15,600 [c]
Br	—	13,400	—	16,700
Cl	13,480	13,850	14,120	—
H	13,420	14,400	15,530	16,100
CH_3	12,450	15,900	14,900	15,800

[a] Alcoholysis in 40 : 60 ethyl alcohol–ether; Nixon and Branch, *J. Amer. Chem. Soc.*, 1936, **58**, 492, 2499. [b] Alcoholysis in pure ethyl alcohol; Norris and Young, *ibid.*, 1935, **57**, 1420. [c] Present work.

The effect of substituents on activation energy has been discussed fully by Hinshelwood, Laidler, and Timm (*loc. cit.*) in terms of electron accession at the seat of reaction. It has been observed that E increases as the strength of the C–Cl bond increases in certain reactions which are thought to be governed by preliminary ionisation. In the alcoholysis of the benzoyl chlorides in alcohol–ether mixtures, however (Nixon and Branch, *J. Amer. Chem. Soc.*, 1936, **58**, 2499), the effect of substituents on E shows it to be governed mainly by the repulsion energy. In this bimolecular reaction, substituents increase the energy of activation in the order, $NO_2 < Br < Cl < H < CH_3 < CH_3O$, as these groups increase the electron density at the seat of reaction in the same order. The present work dealing with the hydrolysis has shown that E remains almost constant with substitution, but is somewhat less for the *p*-CH_3 *and* *p*-NO_2-compounds than for the unsubstituted chloride. This indicates that in the hydrolysis of unsubstituted benzoyl chloride the C–Cl bond strength and the repulsion energy contribute equally to the activation energy.

In a highly aqueous medium, therefore, reaction may proceed either by unimolecular solvolysis or by bimolecular substitution. Thus methyl substitution increases the rate and decreases E, as reaction proceeds mainly by the ionisation mechanism, whereas the nitro-group increases the rate by promoting the bimolecular reaction. The possibility of this change in mechanism has been discussed briefly by Hughes (*Trans. Faraday Soc.*, 1941, **37**, 601), to explain the effect of substitution on the rate of solvolysis in pure alcohols.

The results for alcoholysis will now be reviewed in greater detail. It is seen from Table II that increasing the ionising power of the solvent changes the order of the activation energies.

TABLE II.

Order of *E*.	Solvent.	*D*, 20°.
$CH_3>H>Cl$	Alcohol 40%, ether 60%	12·8
$H>CH_3>Cl$	Alcohol 100%	25·7
$Br>H>CH_3$	Water 50%, acetone 50%	51·2

In a solution of low alcohol content, the methyl-substituted chloride is apparently hydrolysed according to a bimolecular mechanism, as also is the unsubstituted chloride, but in pure alcohol the unimolecular mechanism preponderates.

On considering the effect of the position of the substituent, it is noted that in the hydrolysis and alcoholysis (Norris and Young, *loc. cit.*; Olivier *et al.*, *loc. cit.*) the rates for the methyl and nitro-compounds change in reverse orders: $o- \gg m- \sim p\text{-}CH_3$; $o- \ll m- \ll p\text{-}NO_2$. Although *ortho*-groups often introduce anomalies in rate (Hughes, *Quart. Reviews*, 1948, **2**, 107), these sequences indicate that the effect of the *o*-methyl group in releasing electrons is much greater than the effect produced by the *m*- or *p*-group, and consequently the unimolecular mechanism is promoted to a greater extent. In the second case, the *m*- and the *p*-nitro-group greatly increase the rate of the bimolecular reaction by removing electrons from the reactive carbon atom. For the *ortho*-compound, however, the rate is decreased considerably owing to the steric hindrance offered by the large nitro-group to an approaching water dipole. It is significant that the activation energy for the alcoholysis, with pure ethyl alcohol, of the *o*-nitro-compound (12·9 kcals.) is much less than that of the *o*-methyl compound (16·5 kcals.), although the rate of alcoholysis of the latter compound is greater than that of the former (Norris and Young, *loc. cit.*).

Finally the peculiar di-*ortho*-effects in the alcoholyses provide strong support for the theory that the benzoyl chlorides may be hydrolysed by alternative mechanisms. Norris and Ware (*J. Amer. Chem. Soc.*, 1939, **61**, 1418) found that 2 : 6- and 2 : 4 : 6-substituents affect the rate in two distinct ways. Positive groups (*i.e.*, electron-repelling with respect to hydrogen), *e.g.*, methyl, methoxy-, and ethoxy-, reacted so fast in the pure alcohol that the actual rate could not be measured. On the other hand negative groups, *e.g.*, nitro-, bromo-, and chloro-, decrease the rate considerably. Here we are concerned with very large differences in rate—much greater than the changes caused by monosubstitution. Steric hindrance has been suggested to explain the large reductions in rate, a similar reduction being observed in the hydrolysis of 2 : 6-dibromobenzoyl chloride (Olivier, *Rec. Trav. chim.*, 1929, **48**, 227).

That steric hindrance is not exhibited by the di- and tri-methyl, -methoxy-, and -ethoxy-compounds shows that these are hydrolysed by a different mechanism, which does not involve the close approach of an attacking molecule. These positive groups in the *ortho*-positions would promote unimolecular solvolysis, the rate of which is unaffected by steric hindrance. In support of this mechanism, Hughes (*loc. cit.*) has observed that hydroxyl ions have very little catalytic effect on the rate of alcoholysis of 2 : 4 : 6-trimethylbenzoyl chloride.

EXPERIMENTAL.

Purification of Materials.—Commercial benzoyl chloride was distilled under reduced pressure several times, and a final fraction (b. p. 196°) obtained by distillation under atmospheric pressure. This was introduced into a conical flask provided with a ground-glass joint and attached to a microburette. The whole of the apparatus was carefully dried before benzoyl chloride was admitted, and all openings to the air were connected to tubes containing calcium chloride and phosphoric oxide.

p-Toluoyl chloride, prepared from *p*-toluic acid by phosphorus pentachloride and purified by distillation at reduced pressure, had b. p. 102°/15 mm.

p-Nitrobenzoyl chloride, prepared from *p*-nitrobenzoic acid in the usual way and purified by repeated recrystallisation from light petroleum (b. p. 60—80°), had m. p. 73°.

p-Bromotoluene and potassium permanganate at 130° (for a day) gave *p*-bromobenzoic acid, m. p. 249°. The acid was refluxed with the calculated quantity of phosphorus pentachloride, and when reaction ceased, extracted with light petroleum (b. p. 60—80°). The crude bromide was recrystallised from light petroleum several times to give a pure product, m. p. 42°.

Large quantities of acetone were purified as follows. 2—3 L. were shaken for 1/2 hour with 100 ml. of 2% potassium permanganate solution containing 20 ml. of concentrated sulphuric acid, and then set aside for several hours; the acetone was distilled off through a 5 ft. Vigreux column. The distillate was treated with 50 ml. of concentrated silver nitrate solution and 20 ml. of 2*N*-sodium hydroxide. After the mixture had been occasionally shaken during several hours, calcium chloride was added and the mixture set aside overnight. The acetone was subsequently decanted into a distillation flask, treated with 20 g. of calcium chloride, and distilled again. The collected fraction, b. p. 56—57°, was allowed to remain overnight in contact with calcium chloride, and fractionated as before, the first 50 ml. being rejected. The final distillate was collected in a bottle fitted with a calcium chloride guard-tube.

Rate Measurement.—The principle of the concentration cell was employed in following the rate of hydrolysis. A silver/silver chloride electrode, immersed in the hydrolysing solution, set up an E.M.F.

which was just opposed by a similar electrode in a solution of hydrochloric acid of known concentration. The electrodes were connected through a galvanometer which was used as a null-point instrument, hydrochloric acid being titrated into the calibration cell. The apparatus is shown diagrammatically in *Fig.* 1.

A small constant-speed electric motor was connected through a small fibre gear-wheel to two large equivalent gears fitted to vertical stainless steel axles. A small steel cup was screwed to the top of each axle, the lower ends of which were fitted to two identical glass stirrers. Equal lengths of chloridised silver wire, of *ca.* 1-mm. diameter, were wound spirally round the stirrers and the upper ends fixed to screw terminals in the steel axles. A thick steel wire was supported in the centre of each steel cup and made electrical contact with a small quantity of mercury placed in each cup. The two steel wires were connected *via* a tapping key to a mirror galvanometer with a sensitivity of the order of 50 mm./m./microamp. The stirrers were allowed to rotate in the centre of two 100-ml. beakers which were connected by means of an agar–salt bridge. One beaker contained the reacting solution, the other being used as the titration cell, and both were fixed in a small thermostatically controlled bath.

Fig. 1.

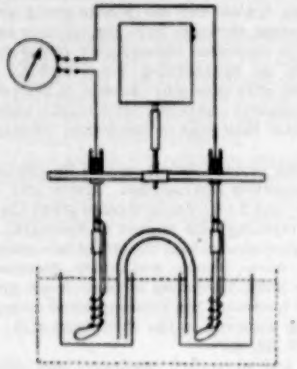
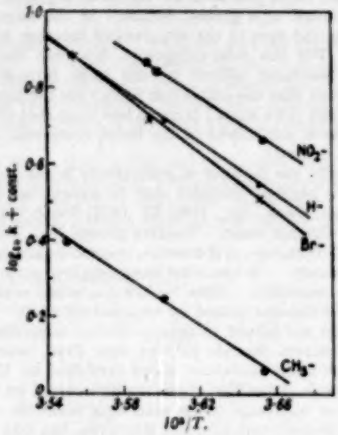


Fig. 2.



In a typical experiment, 25 ml. of 0·45*N*-potassium nitrate were pipetted into each beaker and stirred slowly until the liquids reached the temperature of the bath. In the meantime two 25-ml. portions of purified acetone, in separate dry boiling tubes, were cooled for ½ hour in an alcohol–carbon dioxide bath at −41·5°. Several drops of benzoyl chloride were added from the storage microburette to one of these samples, so that the approximate concentration was known. The acetone was then quickly added to the nitrate solution in the titration cell, followed by a known volume (1 drop) of standard hydrochloric acid. The reaction was then started by rapid addition of the cooled solution of benzoyl chloride in acetone to the other beaker. A stop watch was started immediately after the addition, which took approx. 1 second, and the time observed when the galvanometer was not deflected. A further drop of hydrochloric acid was added from the microburette to the calibration cell and a second balance time obtained, this procedure being continued until the sensitivity of the system became too low for accurate measurements.

At the end of the experiment, the hydrolysing solution was transferred to a 400-ml. beaker and analysed gravimetrically as silver chloride. The reactions were performed in the presence of potassium nitrate to eliminate solution junction potentials as far as possible.

Similar procedures were adopted in the experiments using substituted benzoyl chlorides. In the case of the two solid derivatives, the samples were weighed directly into the cooled acetone solutions.

The chief difficulty encountered in these experiments was the temperature control, owing to the large heat of mixing of acetone and water. Thus the acetone had to be pre-cooled to −41·5° to obtain a final temperature of *ca.* 0°, so that in no two cases could the temperature be exactly reproduced. In the following results the rate constants are corrected in some cases to obtain 0° values where comparisons are required, utilising the experimentally determined temperature coefficient.

Results.—(a) *The effect of hydrogen ions.* Small quantities of nitric acid were added to the reaction mixture and also to the titration cell, and the rate of hydrolysis was determined. Control experiments in the absence of nitric acid, but with small known quantities of added water, were performed to determine the accelerating influence of the water in the added nitric acid solution. Table III shows that there is no difference in rate in the presence of hydrogen ions, in agreement with previous observations of Olivier and Berger (*loc. cit.*).

TABLE III.

Temp., °c.	Normality of C_6H_5·COCl.	Normality of HNO_3.	Vol. of H_2O (ml.).	k_1, min.$^{-1}$.	k_1 (corr.), min.$^{-1}$.
0·7	0·00833	0·0073	0·323	0·0346	0·0322
0·9	0·00860	0·0137	0·596	0·0367	0·0336
0·6	0·0147	0·0137	0·596	0·033	0·0310
0·8	0·0109	0·027	1·179	0·0361	0·0333
0·7	0·0093	—	0·323	0·0340	0·0316
0·7	0·0124	—	0·596	0·0355	0·0330
0·7	0·00985	—	1·178	0·0365	0·0340

Thus in contrast to several other similar compounds containing a highly labile chlorine atom (cf. Böhme, *Ber.*, 1941, **74**, 248; Leimu and Salomaa, *Acta Chem. Scand.*, 1947, **1**, 353) there is no evidence of hydrogen-ion catalysis in the acid hydrolysis of benzoyl chloride. From the results in the above table, and from many other experiments, it was found that the rate of reaction is almost independent of benzoyl chloride concentration in the range 0·004—0·02N.

(b) *The effect of hydroxyl ions.* See Table IV.

TABLE IV.

Temp., °c.	C_6H_5·COCl (*a*).	NaOH (*b*).	$t_{\frac{1}{2}}$ (mins.).	Initial rate.*	k_2, l./g.-mol./min.
0·8	0·0038	0·0062	17—50	0·0401	0·82
0·8	0·0075	0·0062	18—0	0·0392	0·70
0·9	0·0129	0·0224	11—10	0·0541	0·85
0·7	0·0224	0·0224	15—0	0·0497	0·67
0·8	—	—	—	—	—

* Fractional decomposition of C_6H_5·COCl (x/a), per min.
$k_1 = 0·035$ min.$^{-1}$. Mean value of $k_2 = 0·76$ l./g.-mol./min.

The bimolecular constant was computed from the limiting rate at zero time, obtained graphically thus:

$$\frac{1}{a}\left(\frac{dx}{dt}\right)_{t=0} = k_1 + k_2 b$$

This approximate method was used because integration of the fundamental equation

$$dx/dt = k_1(a - x) + k_2(a - x)(b - x)$$

leads to the following complex solution which cannot be used directly to determine k_2:

$$t = \frac{1}{k_1 + k_2(b - a)} \ln \frac{a}{a - x} - \ln \frac{k_1 + k_2 b}{k_1 + k_2(b - x)}$$

It is seen that for 50% aqueous-acetone mixtures, the ratio $k_2/k_1 = 20$, the significance of which has been discussed above.

(c) *Temperature and substituents.*

TABLE V.

	Temp., °c.	k_1, min.$^{-1}$.	E (±300 cals.).	$\log_{10} B$.
Benzoyl chloride	0·7	0·0350	16,100	9·5
	4·4	0·0525		
	8·3	0·0770		
p-Bromobenzoyl chloride	0·7	0·0320	16,700	9·9
	5·0	0·0518		
	9·0	0·0770		
p-Nitrobenzoyl chloride	0·5	0·460	15,600	10·3
	4·7	0·692		
	5·0	0·750		
p-Toluoyl chloride	0·5	0·115	15,800	9·8
	4·5	0·177		
	8·5	0·280		

Detailed results of velocity constants at three temperatures are given in Table V, and the graphs of $\log_{10} k_1$ against $1/T$ in Fig. 2. Table V also includes values of the activation energy E and frequency factor B, determined graphically by application of the simple Arrhenius equation, $\ln k_1 = (-E/RT) + \ln B$. The significance of these activation energies has already been discussed.

We thank Prof. J. R. Partington for his interest and advice, Dr. R. F. Garwood with whom several helpful discussions were held, and the Central Research Fund for financial assistance.

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, March 18th*, 1950.]

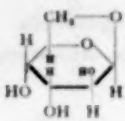
351. *The* iso*Propylidene Derivatives of* D-*Altrose and* 1 : 6-*Anhydro*-β-D-*altrose.*

By F. H. Newth and L. F. Wiggins.

When the equilibrium mixture of D-altrose and 1 : 6-anhydro-β-D-altrose is treated with acetone in the presence of sulphuric acid, three isopropylidene derivatives are obtained: **3** : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose, 1 : 2-3 : 4- and 1 : 2-5 : 6-di*iso*propylidene D-altrose. Evidence is presented which demonstrates the constitution of the first two of these compounds. The third is identical with the compound which Steiger and Reichstein (*Helv. Chim. Acta*, 1936, **19**, 1011) obtained by the treatment of D-altrose itself with acetone.

It was shown by Hudson and Richtmyer (*J. Amer. Chem. Soc.*, 1935, **57**, 1716) that, in acid solution, altrose gives rise to an equilibrium mixture of the sugar itself and 1 : 6-anhydro-β-D-altropyranose (I), the latter compound being later (*idem*, *ibid.*, 1940, **62**, 961) isolated in crystalline form. A study has now been made of the products which are obtained when this mixture of D-altrose and 1 : 6-anhydro-β-D-altrose is condensed with acetone.

The starting material (*A*) was obtained by the acid hydrolysis of 4 : 6-benzylidene α-methyl-D-altroside (II), prepared from 4 : 6-benzylidene 2 : 3-anhydro-α-methyl-D-alloside. It was a syrup which showed a specific rotation practically identical with that recorded by Hudson and Richtmyer for the product obtained by the treatment of D-altrose with hydrochloric acid. That 1 : 6-anhydro-β-D-altrose was indeed present was shown by acetylation of the mixture and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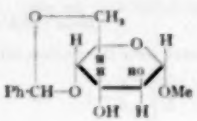
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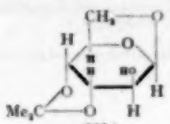
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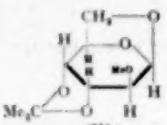
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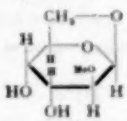
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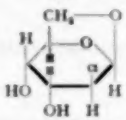
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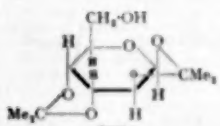
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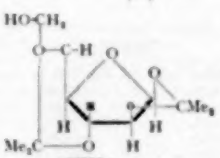
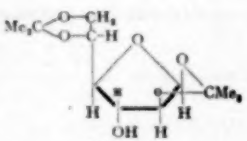

(VIII.)


(IX.)

crystallisation, from the product, of **2** : **3** : 4-triacetyl 1 : 6-anhydro-β-D-altrose. Deacetylation of this gave a syrup from which crystalline 1 : 6-anhydro-β-D-altrose separated after seeding with an authentic specimen kindly provided by Dr. N. K. Richtmyer. 1 : 6-Anhydro-β-D-altrose and acetone containing a small amount of sulphuric acid gave **3** : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose* (III), the structure of which was established by the following observations. With silver oxide and methyl iodide it gave a monomethyl derivative, **2**-*methyl* **3** : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose* (IV), which was hydrolysed by acetic acid to **2**-*methyl* 1 : 6-*anhydro*-β-D-*altrose* (V). When this substance was oxidised with lead tetra-acetate (Hockett and McClenahan, *J. Amer. Chem. Soc.*, 1939, **61**, 1667), the reaction followed the normal course for a compound containing one *cis*-glycol group, one atomic proportion of oxygen being rapidly consumed (see figure). Hence, in (III), the isopropylidene residue must be allocated to $C_{(3)}$ and $C_{(4)}$. Moreover, the 2-chloro **3** : 4-diacetyl 1 : 6-anhydro-**2**-deoxy-β-D-altrose of known structure described by Newth, Overend, and Wiggins (*J.*, 1947, 10), on deacetylation, gave crystalline **2**-*chloro*-1 : 6-*anhydro*-**2**-*deoxy*-β-D-*altrose* (VI), which behaved in the same way with lead tetra-acetate

(see figure). Treatment of (III) with toluene-*p*-sulphonyl chloride led to the isolation of 2-*toluene*-p-*sulphonyl* 3 : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose*.

The reaction of the equilibrium mixture (*A*) with acetone in the presence of sulphuric acid produced a mixture of liquid *iso*propylidene derivatives. With toluene-*p*-sulphonyl chloride in pyridine this gave crystalline 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose, identical with the compound described above, in yield corresponding very closely with that expected from the work of Hudson and Richtmyer on the equilibrium mixture of D-altrose and 1 : 6-anhydro-β-D-altrose; reductive removal of the toluene-*p*-sulphonyl group with sodium amalgam in alcohol afforded smoothly 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (III). After separation of the crystalline toluene-*p*-sulphonyl derivative, the residual syrup (*B*) was treated with sodium iodide in acetone at 110°. Sodium toluene-*p*-sulphonate was precipitated, which indicated the detachment of a toluene-*p*-sulphonyl residue from a primary alcohol group. Sodium amalgam in alcohol removed the toluene-*p*-sulphonyl groups and the product was found to contain two di*iso*propylidene derivatives of D-altrose. The first was a liquid, non-reducing *diisopropylidene* D-*altrose* which gave a carboxylic acid on oxidation with alkaline permanganate. This acid still contained two *iso*propylidene residues and gave a positive naphtharesorcinol test for uronic acids, a liquid *methyl* ester, and a crystalline *amide*. The di*iso*propylidene altrose must therefore possess a free hydroxyl group at $C_{(3)}$. Depending on whether altrose in this compound has the pyranose or furanose structure, the di*iso*propylidene residues must involve $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and (*a*) $C_{(4)}$ or (*b*) $C_{(5)}$. On the assumption that altrose here exists in the pyranose modification there are three possible allocations of the *iso*propylidene residues, namely to positions 1 : 3-2 : 4, 1 : 2-3 : 4 (VII), or 1 : 4-2 : 3. Scale models show that of these only (VII) is sterically possible. If, however, D-altrose assumed the furanose modification, then 1 : 2-3 : 5 (VIII), 1 : 5-2 : 3, or 1 : 3-2 : 5 would be theoretically possible positions for the attachment of the *iso*propylidene residues, but of these only (VIII) is at all probable on steric grounds. Although there is a precedent for the 3 : 5-allocation of an *iso*propylidene group as in (VIII) because Ohle and Vargha (*Ber.*, 1928, **61**, 1203) prepared 6-toluene-*p*-sulphonyl 1 : 2-3 : 5-di*iso*propylidene D-glucofuranose from 6-toluene-*p*-sulphonyl 1 : 2-*iso*propylidene D-glucofuranose, it was only possible to prepare such a compound when ketal formation on adjacent carbon atoms was prohibited. Therefore, although the liquid compound, on the evidence at present available, may be either 1 : 2-3 : 4-di*iso*propylidene D-altropyranose (VII) or 1 : 2-3 : 5-di*iso*propylidene D-altrofuranose (VIII), we favour the former, but further work is required to prove this contention definitely.

The crystalline component of the syrup (*B*) was the 1 : 2-5 : 6-di*iso*propylidene D-altrofuranose (IX) obtained from D-altrose itself by Steiger and Reichstein (*Helv. Chim. Acta*, 1936, **19**, 1011) who indicated its structure.

Experimental.

Hydrolysis of 4 : 6-*Benzylidene* α-*Methyl*-D-*altroside*.—This substance (40 g.; Hudson and Richtmyer, *J. Amer. Chem. Soc.*, 1941, **63**, 1716) was dissolved in 5% sulphuric acid (400 c.c.), and the solution boiled under reflux for 17 hours and, when cool, extracted with ether to remove benzaldehyde. It was then made slightly alkaline with barium hydroxide and immediately neutralised with carbon dioxide. The solution was filtered, the residue was washed with water, and the filtrate and washings were evaporated under diminished pressure to a syrup (24·0 g.) containing a mixture of D-altrose and 1 : 6-anhydro-β-D-altrose and showing $[\alpha]_D^{20}$ −94·6° in water (*c*, 2·98). Hudson and Richtmyer (*J. Amer. Chem. Soc.*, 1935, **57**, 1721) give $[\alpha]_D$ −98·2° for this mixture. A portion (6 g.) of the syrup, acetylated in the manner described by the above authors, gave 2 : 3 : 4-triacetyl 1 : 6-anhydro-β-D-altrose (5·5 g.), m. p. 99—100° after recrystallisation from alcohol.

Deacetylation of 2 : 3 : 4-*Triacetyl* 1 : 6-*Anhydro*-β-D-*altrose*.—The above triacetyl derivative (2 g.) was dissolved in dry methyl alcohol (10 c.c.) and a trace of sodium added. After being kept overnight, the solution was evaporated to give 1 : 6-anhydro-β-D-altrose as a clear syrup (1·2 g.). A small portion crystallised completely when seeded with an authentic specimen kindly provided by Dr. N. K. Richtmyer. When recrystallised from ethyl acetate, prisms were obtained which had m. p. 58—59° and $[\alpha]_D^{20}$ −195° in water (*c*, 0·49). The m. p. in admixture with the authentic specimen showed no depression. The sample provided by Dr. Richtmyer had m. p. 58—61° and $[\alpha]_D^{20}$ −185° in water (*c*, 1·16). Hudson and Richtmyer (*J. Amer. Chem. Soc.*, 1939, **61**, 214) described 1 : 6-anhydro-β-D-altrose as having m. p. 135°, but with signs of melting at 80—90°, and $[\alpha]_D$ −215° in water.

3 : 4-iso*Propylidene* 1 : 6-*Anhydro*-β-D-*altrose*.—The 1 : 6-anhydro-β-D-altrose syrup (1·0 g.) obtained on deacetylation of the crystalline triacetate was shaken overnight with acetone (20 c.c.) containing concentrated sulphuric acid (0·1 c.c.). After neutralisation of the acid with anhydrous sodium carbonate, the inorganic residue was removed by filtration and washed with acetone. The combined filtrate and washings were evaporated and a syrup (1·1 g.) was obtained, having b. p. 158° (bath temp.)/0·05 mm. The colourless distillate (0·7 g.) showed $[\alpha]_D^{20}$ −160° in chloroform (*c*, 7·56) and n_D^{20} 1·4879 and subsequently crystallised. The 3 : 4-iso*propylidene* 1 : 6-*anhydro*-β-D-*altrose* recrystallised from ether–light petroleum in prisms, m. p. 84—85°, $[\alpha]_D^{20}$ −171° in chloroform (*c*, 1·0) (Found: C, 53·2; H, 6·7. $C_9H_{14}O_5$ requires C, 52·9; H, 6·8%).

2-*Toluene*-p-*sulphonyl* 3 : 4-iso*Propylidene* 1 : 6-*Anhydro*-β-D-*altrose*.—3 : 4-*iso*Propylidene 1 : 6-

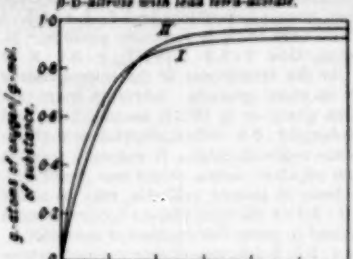
anhydro-β-D-altrose (1·3 g.) was dissolved in dry pyridine (10 c.c.), and toluene-*p*-sulphonyl chloride (1·7 g.) added. After being kept overnight, the mixture was poured into water, whereupon a crystalline product separated. This, recrystallised from alcohol, formed plates, m. p. 176—177°, $[\alpha]_D^{20}$ −150·8° in chloroform (*c*, 2·24) (Found: C, 53·7; H, 5·7. $C_{16}H_{20}O_7S$ requires C, 53·9; H, 5·6%).

Reduction of 2-*Toluene-p-sulphonyl* 3 : 4-iso*Propylidene* 1 : 6-*Anhydro-β-*D-*altrose with Sodium Amalgam.*—The substance (10 g.) was suspended in 90% methyl alcohol (200 c.c.) containing 3% sodium amalgam (200 g.). The mixture was stirred at 45° for 4 hours and then kept overnight. The solution was decanted from the mercury which was washed with methyl alcohol. The combined solution and washings were neutralised with carbon dioxide, and the inorganic precipitate was filtered off and washed. The dry residue which was obtained when the combined filtrate and washings were evaporated was extracted with chloroform. Removal of the solvent left a syrup which crystallised spontaneously. Recrystallisation from ether–light petroleum gave 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (4·9 g.), m. p. 83—85°.

2-*Methyl* 3 : 4-iso*Propylidene* 1 : 6-*Anhydro-β-*D-*altrose.*—3 : 4-*iso*Propylidene 1 : 6-anhydro-β-D-altrose (0·30 g.) was treated with dry silver oxide and methyl iodide at 45° for 12 hours. The methyl iodide was removed by evaporation and the dry residue extracted with boiling chloroform six times. The solvent was evaporated and the residue treated twice more with the methylating reagents. Final evaporation of the solvent gave a syrup which distilled at 110° (bath temp.)/0·01 mm. as a colourless liquid (0·20 g.). It was 2-*methyl* 3 : 4-*isopropylidene* 1 : 6-*anhydro-β-*D-*altrose* which showed n_D^{20} 1·4689 and $[\alpha]_D^{20}$ −140° in chloroform (*c*, 0·85) (Found: C, 55·5; H, 7·3. $C_{10}H_{18}O_5$ requires C, 55·5; H, 7·4%).

2-*Methyl* 1 : 6-*Anhydro-β-*D-*altrose.*—2-Methyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (0·25 g.) was boiled under reflux with 20% acetic acid (5·0 c.c.) for 3 hours. Dissolution was then complete. Evaporation under diminished pressure afforded a syrup which distilled as a colourless liquid (0·08 g.) at 165° (bath temperature)/0·04 mm. The 2-*methyl* 1 : 6-*anhydro-β-*D-*altrose* showed n_D^{20} 1·4692 and $[\alpha]_D^{20}$ −198° in alcohol (*c*, 1·03) (Found: C, 47·2; H, 6·6. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8%).

Rates of oxidation of derivatives of 1 : 6-*anhydro-β-*D-*altrose with lead tetra-acetate.*



I. 2-*Methyl* 1 : 6-*anhydro-β-*D-*altrose.*
II. 2-*Chloro* 1 : 6-*anhydro-2-deoxy-β-*D-*altrose.*

Oxidation of 2-*Methyl* 1 : 6-*Anhydro-β-*D-*altrose with Lead Tetra-acetate.*—To the substance (0·0568 g.) dissolved in glacial acetic acid (49 c.c.) was added standard lead tetra-acetate solution (50 c.c.) (prepared according to the method of Hockett and McClenahan, *loc. cit.*). Acetic acid was added to make the solution up to 100 c.c. 10-C.c. portions were withdrawn at intervals and run into 20 c.c. of a buffer solution containing sodium acetate (250 g./l.) and potassium iodide (20 g./l.). The iodide liberated was titrated with 0·02*N*-sodium thiosulphate solution. See figure.

2-*Chloro*-1 : 6-*anhydro*-2-*deoxy-β-*D-*altrose.* — 2-Chloro-3 : 4-diacetyl 1 : 6-anhydro-2-deoxy-β-D-altrose (0·71 g.), prepared according to Newth, Overend, and Wiggins (*loc. cit.*), was dissolved in dry methyl alcohol (10 c.c.), and a trace of sodium added. After being kept overnight the solution was evaporated to give a crystalline residue. 2-*Chloro*-1 : 6-*anhydro*-2-*deoxy-β-*D-*altrose*, recrystallised from ethyl acetate, formed clusters of plates (0·40 g.), m. p. 122—123°, $[\alpha]_D^{20}$ −224° in alcohol (*c*, 1·045) (Found: C, 40·1; H, 5·0. $C_6H_9O_4Cl$ requires C, 40·0; H, 5·0%).

Oxidation of 2-*Chloro*-1 : 6-*anhydro*-2-*deoxy-β-*D-*altrose with Lead Tetra-acetate.*—The substance (0·0756 g.) was oxidised with lead tetra-acetate in the manner described above (see also figure).

Treatment of the D-*Altrose*-1 : 6-*Anhydro-β-*D-*altrose Mixture with Acetone.*—The syrupy mixture (25 g.) was shaken with acetone (400 c.c.) containing concentrated sulphuric acid (2·2 c.c.) for 24 hours. The acid was then neutralised with anhydrous sodium carbonate, the solution was filtered, and washed, and the combined filtrate and washings were evaporated. The product (31 g.) was dissolved in pyridine (150 c.c.), and toluene-*p*-sulphonyl chloride (30 g.) added. After being kept for 24 hours, the mixture was poured into water and the crystalline precipitate which separated recrystallised from alcohol, giving 3-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose (23 g.), m. p. 170—173°, identical with the product obtained as above. Complete evaporation of the mother-liquors gave a syrup (*B*) (18·5 g.) which could not be crystallised.

Treatment of Syrup (B) *with Sodium Iodide in Acetone.*—The syrup (*B*) (1 g.) was dissolved in dry acetone (200 c.c.) containing dry sodium iodide (1 g.), and the solution heated at 110° for 5 hours; 0·2 g. of sodium toluene-*p*-sulphonate separated, which corresponds with 0·4 primary toluene-*p*-sulphonyl group. The solution was evaporated and the residue extracted with chloroform. The extract was washed with sodium thiosulphate solution, dried ($MgSO_4$), and evaporated. A syrup (0·8 g.) was obtained from which no crystalline product has been separated.

Reduction of Syrup (B) *with Sodium Amalgam.*—The syrup (*B*) (18·5 g.) remaining after the removal of 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene 1 : 6-anhydro-β-D-altrose was dissolved in 90% methyl alcohol (300 c.c.), and 3% sodium amalgam (100 g.) added. After being stirred overnight, the solution was decanted from the mercury and neutralised with carbon dioxide. It was then evaporated to dryness and the residue extracted with ether. Evaporation of this extract gave a syrup (6·8 g.) which was fractionally distilled through a Widmer column. Three fractions were collected: (i) B. p. 128—130° (bath temp.)/0·01 mm. (0·65 g.), $[\alpha]_D^{20}$ −13·1° in chloroform (*c*, 1·30), n_D^{20} 1·4370; this was 1 : 2-3 : 4-*diiso-propylidene* D-*altropyranose* (Found: C, 55·1; H, 7·5. $C_{12}H_{20}O_6$ requires C, 55·4; H, 7·7%); when dissolved in water, it did not reduce Fehling's solution. (ii) B. p. 140—150° (bath temp.)/0·01 mm. (1·34 g.), $[\alpha]_D^{20}$ −1·7° in chloroform (*c*, 1·19), n_D^{20} 1·4615; this partly crystallised when kept and contained

some 1 : 2-5 : 6-*diisopropylidene* D-altrofuranose. (iii) B. p. 152—170° (bath temp.)/0·01 mm. (3·05 g.); this crystallised completely and on recrystallisation from ether–light petroleum 1 : 2-5 : 6-diisopropylidene D-altrofuranose was obtained having m. p. 87—88° and $[\alpha]_D^{20}$ +25·7° in acetone (*c*, 1·04) (Found: C, 55·0; H, 7·9. Calc. for $C_{12}H_{20}O_6$: C, 55·4; H, 7·7%); Steiger and Reichstein (*loc. cit.*) give m. p. 89° and $[\alpha]_D$ +28·3° in acetone.

Oxidation of 1 : 2-3 : 4-*Diisopropylidene* D-*Altropyranose with Permanganate.*—The substance (1·4 g.) was dissolved in 0·1N-sodium hydroxide (128 c.c.), and potassium permanganate (1·62 g.) added. The solution was set aside overnight, during which time it became colourless and a precipitate of manganese oxide formed. Carbon dioxide was passed into the filtered solution until it was neutral. The solution was then evaporated to dryness under diminished pressure and the residue extracted with cold absolute alcohol. Evaporation of the extract gave a glass (1·15 g.). This was dissolved in 0·1N-sulphuric acid (39 c.c., 1 equiv.), and the solution extracted 6 times with ether. The extract was dried ($MgSO_4$) and evaporated. A syrupy acid (1·05 g.) was obtained which gave a strongly positive naphtharesorcinol test for uronic acids.

The acid (1·05 g.) was dissolved in ether, and ethereal diazomethane added. A vigorous evolution of nitrogen occurred. The solution was set aside overnight in the presence of excess of diazomethane and then evaporated. The syrup obtained distilled at 105° (bath temp.)/0·01 mm. as a clear liquid, showing n_D^{20} 1·4565 and $[\alpha]_D^{20}$ +18·0° in chloroform (*c*, 1·22). It was *methyl* 1 : 2-3 : 4-*diisopropylidene* D-*altruronate* (Found: C, 54·4; H, 7·2. $C_{13}H_{20}O_7$ requires C, 54·2; H, 6·9%).

A solution of this ester (0·1 g.) in dry methyl alcohol (5 c.c.) was saturated with ammonia at 0°. After 36 hours, it was evaporated in a desiccator, the residue slowly crystallising. The *amide*, recrystallised from ether–light petroleum, had m. p. 115—116°, $[\alpha]_D^{20}$ −9·4° in acetone (*c*, 0·95) (Found: C, 53·2; H, 7·0. $C_{12}H_{19}O_6N$ requires C, 52·8; H, 7·0%).

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352. *The Structure of β-Hydrojuglone and Related Compounds. Keto–Enols of the Naphthalene Series.*

By R. H. Thomson.

β-Hydrojuglone is shown to be 5-hydroxy-1 : 4-diketo-1 : 2 : 3 : 4-tetrahydronaphthalene (IV). The simplest members of this series (VI; R = H or Me) are stable compounds, but in general these diketones exhibit few ketonic properties; under most reaction conditions they enolise rapidly and only derivatives of the corresponding polyhydroxynaphthalenes are obtained.

Juglone (5-hydroxy-1 : 4-naphthaquinone) occurs in walnut tissues in a reduced form and may be isolated by solvent-extraction and oxidation. Two isomeric reduction products, α- and β-hydrojuglone, were isolated by Mylius (*Ber.*, 1884, **17**, 2441; 1885, **18**, 2567) and their existence as glycosides was postulated by early workers. Daglish (*Biochem. J.*, in the press) has now identified the 5-glucoside of α-hydrojuglone as a natural product, but careful examination of a large number of walnut extracts by chromatographic and spectrographic analysis failed to detect the β-isomer or a derivative. Mylius, in fact, is the only worker who has obtained β-hydrojuglone from natural sources, and the present work shows that his method of extraction would convert part of the α-hydrojuglone into the β-form.

Mylius showed that α-hydrojuglone was readily transformed into the β-isomer by heating it above its melting point; both isomers formed the same triacetate and the same tribenzoate, but, whereas the α-compound was readily oxidised to juglone and was therefore (I), β-hydrojuglone was not a quinol. Later, Willstätter and Wheeler (*Ber.*, 1914, **47**, 2796) observed that β-hydrojuglone formed monocarbonyl derivatives, indicating that the hydrojuglones were keto–enol tautomers, and they proposed structure (II) or (III) for β-hydrojuglone. Similar

(I.)

(II.)

(III.)

(IV.)

(V.)

(VI.)

substances have been obtained from naphthazarin (5 : 8-dihydroxy-1 : 4-naphthaquinone). Thus Zincke and Schmidt (*Annalen*, 1895, **286**, 27) reduced naphthazarin with acid stannous chloride and obtained a product which they believed to be a tetrahydroxynaphthalene. Wheeler and Edwards (*J. Amer. Chem. Soc.*, 1916, **38**, 387) demonstrated the ketonic character

of this substance by the preparation of a series of monocarbonyl derivatives and an impure bisphenylsemicarbazone, and the structure 5 : 8-dihydroxy-1 : 4-diketo-1 : 2 : 3 : 4-tetrahydronaphthalene (V) was confirmed when Zahn and Ochwat (*Annalen*, 1928, **462**, 72) synthesised the material by condensing quinol with succinic anhydride. On these grounds Zahn and Ochwat (in a footnote to the same paper) proposed the diketo-structure (IV) for β-hydrojuglone. This is now confirmed.

Analogous "β-hydronaphthaquinones" have been prepared by Madinaveitia and Olay (*Anal. Fis. Quim.*, 1933, **31**, 134) and Olay (*Rev. Acad. Cienc. Madrid*, 1935, **32**, 384) from 1 : 4-naphthaquinone, 2-methyl-1 : 4-naphthaquinone, and 5-hydroxy-2-methyl-1 : 4-naphthaquinone (plumbagin), by fusion of their normal quinols. As these compounds formed monocarbonyl derivatives, and attempts to prepare diketo-derivatives were unsuccessful, they were considered to be half-enolised quinones of the same type as (II), or, less likely, (III). The products from 1 : 4-naphthaquinone and 2-methyl-1 : 4-naphthaquinone have now been re-examined, along with β-hydrojuglone (plumbagin was not available). By analogy with Zahn and Ochwat's suggestion these compounds should have the diketone structure (VI; R = H or Me).

The structures put forward by Willstätter and Wheeler, and by Olay, contain enolic hydroxyl groups but very little evidence has been obtained in favour of this. With two exceptions, all the tests applied (see Experimental section) were negative. Attempts to prepare hydroxyl derivatives failed unless catalysts were used which brought about complete enolisation. The compounds dissolve slowly in dilute sodium hydroxide solution (much faster than anthrone however), but this is obviously preceded by enolisation since the ketones may be quantitatively converted into the enols by dissolution in cold dilute alkali followed by acidification. Determination of active hydrogen gave some indication of the presence of a hydroxy-group but the results were anomalous and will be discussed later. Although β-hydrojuglone contains a phenolic group it fails to react with diazomethane or with phenyl *iso*cyanate in absence of a catalyst. This is parallel to the behaviour of juglone and may be ascribed to intramolecular hydrogen bonding.

The failure of the earlier workers to prepare dicarbonyl derivatives from these keto-compounds has been encountered again, but di-*p*-nitrophenylhydrazones have been obtained from Olay's ketones (VI; R = H or Me). Positive chemical proof of the diketo-structure of β-hydrojuglone has not been obtained, but substantial evidence is provided by the absorption spectra.

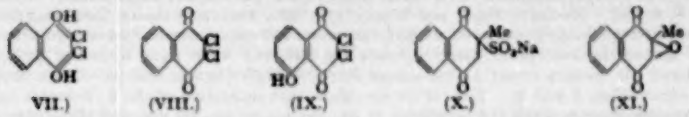
The infra-red absorption of the three ketones and the corresponding 1 : 4-naphthaquinones have been determined for a mull with liquid paraffin. The results are presented in the Table (for the spectra of 1 : 4-naphthaquinone and 2-methyl-1 : 4-naphthaquinone, cf. Rosenkrantz, *J. Biol. Chem.*, 1948, **173**, 441) :

Compound.	Frequency (cm.$^{-1}$). C=O.		OH.	Compound.	Frequency (cm.$^{-1}$). C=O.		OH.
(IV)	1677	1628	Absent	Juglone	1667	1643	Absent
(VI; R = H)	1673		,,	1 : 4-Naphthaquinone	1660		,,
(VI; R = Me) ...	1688		,,	2-Methyl-1 : 4-naphthaquinone	1661		,,

The important features of the spectra from which conclusions may be drawn are the positions of the characteristic carbonyl and hydroxyl bands in the 6-μ. and 3-μ. regions respectively. The spectra of the ketones and the corresponding quinones show only minor differences in these regions, and in all cases, including β-hydrojuglone, there is no hydroxyl band in the spectrum near 3400 cm.$^{-1}$. This eliminates the enolic structures suggested by Olay, and Willstätter and Wheeler, and the compounds must therefore have the 1 : 4-diketo-1 : 2 : 3 : 4-tetrahydronaphthalene structures (IV and VI; R = H or Me). It was considered that the monoketo-form might possibly exist to some extent when the compounds were in solution and not in the crystalline state. However examination of Olay's compounds in dilute carbon tetrachloride solution (2%) showed again the absence of a hydroxyl band. The suppression of the hydroxyl band in juglone and β-hydrojuglone is caused by intramolecular hydrogen bonding and has been observed previously in *peri*-hydroxy-1 : 4-naphthaquinones (Weiss and Ford, *Arch. Biochem.*, 1949, **22**, 288) and *peri*-hydroxyanthraquinones (Flett, *J.*, 1948, 1441). The carbonyl stretching vibration frequency is also affected in such compounds, and juglone and β-hydrojuglone, like 1-hydroxyanthraquinone, show two carbonyl frequencies.

Further evidence in support of the structure of these diketones is obtained from their ultra-violet absorption spectra. The spectra of naphthaquinone dichloride (VIII) and juglone

dichloride (IX) were determined for comparison. Figs. 1—3 show that the curves of Olay's ketones (VI; R = H or Me) are similar to that of (VIII), and the absorption characteristics



VII.) (VIII.) (IX.) (X.) (XI.)

of β-hydrojuglone are of the same type as those of (IX), indicating their structural similarity. Furthermore, Carmack, Moore, and Balis (*J. Amer. Chem. Soc.*, 1950, **72**, 844) have shown

Fig. 1. Fig. 2.

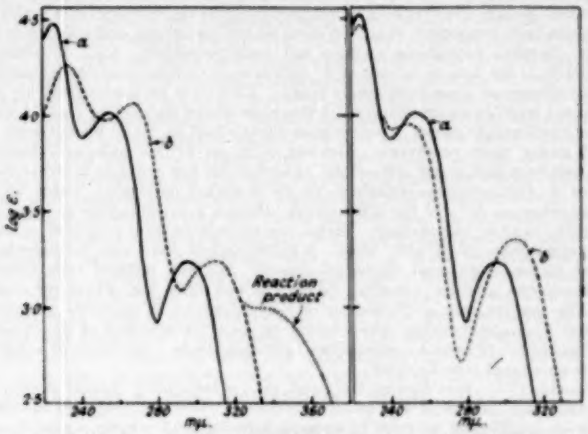
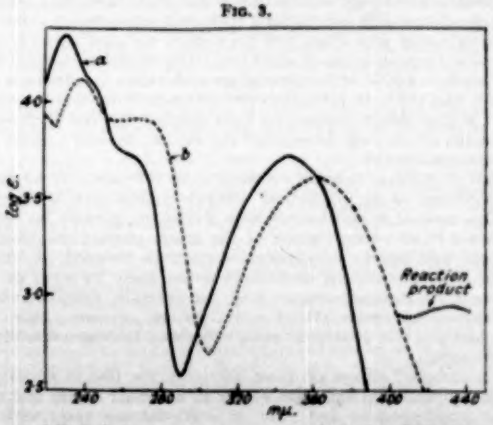


Fig. 1.—*a*, 1 : 4-*Diketo*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. *b*, 1 : 4-*Naphthaquinone dichloride*.
Fig. 2.—*a*, 1 : 4-*Diketo*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. *b*, *β-Hydrojuglone acetate*.

Fig. 3.



a, *β-Hydrojuglone*. *b*, *Juglone dichloride*.

recently that the antihæmorrhagic sodium hydrogen sulphite addition product of 2-methyl-1 : 4-naphthaquinone has structure (X) since its absorption spectrum is very similar to that of 2-methyl-1 : 4-naphthaquinone 2 : 3-oxide (XI). Both curves are very similar to that of (VI; R = Me). Macbeth, Price, and Winzor (*J.*, 1935, 325) have shown that the spectra of simple 1 : 4-naphthaquinones have a maximum at *ca.* 330 mμ.: introduction of a *peri*-hydroxyl group moves the absorption bands towards the red, but when such hydroxyl groups are acetylated the spectra revert to the simple form. β-Hydrojuglone and its acetate show the same effect (Figs. 2 and 3). The curves also show that saturation of the 2 : 3-double bond of the naphthaquinones shifts the maximum at *ca.* 330 mμ. to *ca.* 300 mμ. and introduces a new band at very short wave-length (225 mμ.). For juglone, saturation of the 2 : 3-double bond moves the peak at 425 mμ. to 347 mμ. and again a new maximum is introduced at a short wave-length (230 mμ.).

Although the ability of naphthols and certain polyhydric phenols to react in the tautomeric keto-form is well known, the existence of simple dihydroxynaphthalenes in a stable diketo-form has not hitherto been recognised, except in cases where the ketonic and enol forms are obtained by different chemical procedures and are not interconvertible. *E.g.*, 1 : 4-naphthaquinone dichloride (VIII) is the ketonic isomer of 2 : 3-dichloro-1 : 4-dihydroxynaphthalene (VII). All attempts to tautomerise these compounds failed. Enol ⟶ keto-conversion by fusion of the enol form is not possible as the diketone decomposes above its melting point, and the reverse change cannot be brought about by solution in dilute alkali as (VIII) immediately loses hydrochloric acid under these conditions. Heating solutions of the halogen compounds in the presence of catalysts and under ultra-violet radiation did not promote tautomerisation.

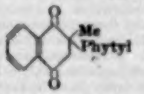
Fusion of 1 : 4-dihydroxynaphthalene, or its 2-methyl derivative, yields an equilibrium mixture containing *ca.* 10% of the diketo-form, whereas α-hydrojuglone is converted into the β-isomer in 67% yield by this method. Reduction of naphthazarin with acid stannous chloride yields a diketone directly in 90% yield. β-Hydrojuglone may also be obtained by direct reduction of juglone with acid stannous chloride, but the method fails completely with 1 : 4-naphthaquinone and its 2-methyl derivative and only the dihydroxy-compounds are obtained. The greater ease of formation of β-hydrojuglone is probably a further effect of intramolecular hydrogen bonding which would enhance the stability of the diketo-form, and this is more marked in (V) which contains two hydrogen bonds. On fusion of α- and β-naphthol in a vacuum no change was detected.

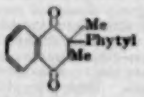
The diketones (VI; R = H and Me), and the corresponding dienols appear to exist in solution as such and there is no sign of an equilibrium. The hydrojuglones on the other hand can exist as an equilibrium mixture in aqueous solution, and α-hydrojuglone may be partly converted into the β-isomer by boiling an aqueous or an aqueous-acid solution, preferably in the presence of a reducing agent to prevent oxidation of the α-form to juglone. When Mylius (*loc. cit.*) isolated both α- and β-juglone from unripe walnut shells the first extraction was carried out with dilute hydrochloric acid containing a little stannous chloride. The aqueous solution obtained was then extracted with ether, and the residue left after removal of the solvent was boiled repeatedly with large amounts of water containing stannous chloride to extract the two hydrojuglones. Clearly isolation of β-hydrójuglone under these conditions is no evidence of its existence in Nature, and the work of Daglish (*loc. cit.*) establishes that β-hydrojuglone is not a natural product. Mylius indeed claimed to have isolated the two hydrojuglones from *ripe* walnut shells, although at one stage he oxidised the extract, isolated juglone, and subsequently reduced it with stannous chloride.

The preparation of hydroxy-diketones analogous to (IV) and (V) by condensing phenols with succinic anhydride in an aluminium chloride–sodium chloride melt is claimed in G.P. 454,762. This method is satisfactory with *p*-dihydric phenols but difficulty would be expected with phenol itself. Examination of the crude product described yielded a little β-salicyloylpropionic acid, but no β-hydrojuglone could be detected. Cyclisation of β-aroylpropionic acids to form naphthalene derivatives is not likely to occur as these compounds readily form lactones. β-Benzoylpropionic acid, for example, forms a lactone when heated alone or with dehydrating agents (Fittig and Ginsberg, *Annalen*, 1898, **299**, 17). When cyclisation of the last acid was attempted using anhydrous hydrogen fluoride the organic acid was recovered unchanged.

Although both carbonyl groups of these diketones are free to enolise, active-hydrogen determinations showed that this takes place only to a limited extent under the Zerewitinoff conditions. Thus β-hydrojuglone and (VI; R = H) did not react with the Zerewitinoff reagent in the cold, but when warmed liberated methane equivalent to 1·53 and 0·95 active

hydrogen atoms respectively; (VI; R = Me) liberated 0·33 equivalent of methane in the cold. Similar results were obtained by Tishler, Fieser, and Wendler (*J. Amer. Chem. Soc.*, 1940, **62**, 1982) with more complex compounds of the same series. By measuring the amount of Grignard reagent consumed *by addition to carbonyl groups* as well as the amount of methane liberated they obtained results corresponding to one hydroxyl group and one carbonyl group in the case of (XII), whereas (XIII) yielded a neglible amount of methane (*i.e.*, virtually no enolisation) but two equivalents of Grignard reagent were used.

(XII.) 



(XIII.)

The simple diketotetrahydronaphthalenes appear at first sight to have promising synthetic applications, but unfortunately the compounds exhibit few ketonic properties, and under most reaction conditions they enolise readily and yield only naphthol derivatives. Thus the diketones (VI; R = H or Me) failed to condense with benzaldehyde or *p*-nitrobenzaldehyde, in contrast to *cyclo*hexane-1 : 4-dione which condenses with benzaldehyde to form 2-benzylquinol (Stollé and Möring, *Ber.*, 1904, **37**, 3487), and Brockmann and Müller (*Annalen*, 1939, **540**, 51) found that the more stable diketone (V) would condense with aliphatic aldehydes, the initial product rearranging to an alkylnaphthazarin. The only products isolated from Grignard and Reformatsky reactions were the corresponding dihydroxynaphthalenes, and reduction with lithium aluminium hydride and the Ponndorf reagent had the same result. Condensation of (VI; R = H) with *p*-nitrosodimethylaniline yielded 2-(*p*-dimethylaminoanilino)-1 : 4-naphthaquinone. Investigation showed that the initial reaction was an oxidation of the enolised diketone to 1 : 4-naphthaquinone, and reduction of the nitroso-compound to *p*-aminodimethylaniline, followed by normal 1 : 4-addition. With (VI; R = Me) reaction with *p*-nitrosodimethylaniline did not proceed beyond the oxidation stage. Madinaveitia (*Anal. Fis. Quim.*, 1933, **31**, 750) has reported that 1 : 4-additions are much more difficult with 2-methyl-1 : 4-naphthaquinone than with 1 : 4-naphthaquinone, and Fries and Lohmann (*Ber.*, 1921, **54**, 2912) observed that 2-methyl-1 : 4-naphthaquinone did not react with aniline. This has been confirmed, and likewise *p*-chloro-, *p*-nitro, and *p*-dimethylamino-aniline failed to react. This is possibly a steric effect as methylamine has been added successfully to 2-methyl-1 : 4-naphthaquinone (Asano and Hase, *J. Pharm. Soc. Japan*, 1941, **61**, 55).

Experimental.

5-Hydroxy-1 : 4-diketo-1 : 2 : 3 : 4-tetrahydronaphthalene (β-Hydrojuglone).—This was prepared (*a*) by Willstätter and Wheeler's method (*loc. cit.*), the intermediate α-hydrojuglone being isolated more conveniently by pouring the ethereal solution through a layer of anhydrous sodium sulphate into light petroleum and collecting the crystalline precipitate rapidly (yield, 67%).

(*b*) A suspension of juglone (1 g.) in dilute hydrochloric acid (250 c.c.; 12%) containing stannous chloride (5 g.) was refluxed for 1 hour, forming a pale yellow solution which was repeatedly extracted with chloroform. After several extractions the yellow colour disappeared but reappeared on storage as the equilibrium was restored. The chloroform solution yielded 0·65 g. of β-hydrojuglone.

(*c*) α-Hydrojuglone (0·5 g.) in dilute hydrochloric acid (50 c.c.; 4%) containing stannous chloride (2·5 g.) was refluxed for 30 minutes. On cooling, the light-yellow solution deposited colourless needles of unchanged α-compound. Chloroform-extraction yielded 95 mg. of the β-isomer (Found: Active H, 0·87%).

β-Hydrojuglone crystallises from hexane in light yellow needles or plates, m. p. 96—97°, and from alcohol in pale yellow leaflets (not colourless, as described by Mylius). The *mono-p-nitrophenylhydrazone* crystallised from a large volume of acetone in small yellow needles, m. p. 270° (decomp. after blackening from 260°) (Found: C, 61·85; H, 4·2; N, 13·9. $C_{16}H_{13}O_4N_3$ requires C, 61·7; H, 4·2; N, 13·5%). A Javanovsky reaction gave a blue-green colour becoming violet. Attempts to prepare a di-*p*-nitrophenylhydrazone by refluxing the compound with excess of reagent in various solvents with and without mineral acid yielded a very insoluble dark purple-brown solid which charred without melting and could not be purified (Found: N, 15·0. $C_{22}H_{16}O_4N_6$ requires N, 18·8%). No satisfactory product could be obtained by using other carbonyl reagents.

1 : 4-Diketo-1 : 2 : 3 : 4-tetrahydronaphthalene.—This was obtained by fusion of 1 : 4-dihydroxynaphthalene in a vacuum according to Olay (*loc. cit.*). It formed colourless leaflets (from hexane), m. p. 98° (10·5%; starting material recovered, 55%) (Found: Active H, 0·63%). The *mono-p-nitrophenylhydrazone* crystallised from alcohol in short orange-red needles, m. p. 253° (decomp.), and gave a blue Javanovsky reaction (Found: C, 65·3; H, 4·5; N, 14·5. $C_{16}H_{13}O_3N_3$ requires C, 65·1; H, 4·4; N, 14·2%). The *di-p-nitrophenylhydrazone* separated from *o*-dichlorobenzene in minute rust-red needles, m. p. 284° (decomp.) (Found: C, 61·7; H, 4·4; N, 19·5. $C_{28}H_{16}O_4N_6$ requires C, 61·4; H, 4·2; N, 19·5%). It gave a violet Javanovsky reaction.

1 : 4-Diketo-2-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene.—This was prepared by Olay's procedure. The

diketone crystallised from hexane in small colourless leaflets, m. p. 60° (11%; 1 : 4-dihydroxy-2-methylnaphthalene recovered, 60%) (Found : Active H, 0·19%. Analysis by Drs. Weiler and Strauss). The *mono-p-nitrophenylhydrazone* crystallised from dilute acetic acid in rust-red small crystals, m. p. 242° (decomp.), and gave a deep-blue Javanovsky reaction (Found : C, 66·3; H, 5·0; N, 13·5. $C_{17}H_{15}O_3N_3$ requires C, 66·0; H, 4·9; N, 13·6%). The *di-p-nitrophenylhydrazone* formed small orange crystals (from aqueous acetone), m. p. 295° (decomp.), and gave a reddish-violet Javanovsky reaction (Found : C, 62·4; H, 4·7; N, 15·8. $C_{23}H_{20}O_5N_6$ requires C, 62·2; H, 4·5; N, 15·9%).

Reactions of the Diketones.—The above diketones failed to give characteristic colour reactions with ferric chloride, sodium nitroprusside, or 3 : 5-dinitrobenzoic acid, dissolved slowly in dilute sodium hydroxide (β-hydrojuglone dissolved rapidly), but gave no indication of unsaturation with bromine. There was no reaction with acetic anhydride during 24 hours at room temperature, or on warming the mixture for 2 hours at 95°, in the absence of a catalyst. On addition of a trace of concentrated sulphuric acid there was an immediate reaction at room temperature. β-Hydrojuglone formed a monoacetate, and the other diketones the corresponding 1 : 4-diacetoxynaphthalenes. All three diketones failed to react with diazomethane. With phenyl *iso*cyanate no reaction took place in boiling xylene (3 hours) in absence of a catalyst, but addition of a drop of triethylamine to a mixture of diketone and phenyl *iso*cyanate caused an immediate reaction at room temperature with formation of the corresponding di- and tri-phenylurethanes. Identical compounds were obtained from the dienols, using the same catalyst.

β-Hydrojuglone acetate. To a stirred suspension of β-hydrojuglone (250 mg.) in acetic anhydride (0·5 c.c.) cooled in ice, a trace of concentrated sulphuric acid was added. The yellow suspension became rapidly colourless. After 10 minutes the acetate was collected, washed with light petroleum, and dried. When crystallised from methanol (charcoal) it formed colourless needles, m. p. 144° (Found : C, 65·7; H, 4·6; Ac, 21·0. $C_{16}H_{14}O_5$ requires C, 66·0; H, 4·6; Ac, 19·7%).

When the acetic anhydride filtrate was stirred with a little ice, a white precipitate was obtained. Crystallisation from dilute acetic acid afforded colourless needles of 1 : 4 : 5-triacetoxynaphthalene, m. p. and mixed m. p. 130°.

1 : 4-*Dihydroxynaphthalenebisphenylurethane* crystallised from alcohol in colourless needles, m. p. 220° (Found : C, 72·0; H, 4·5; N, 6·9. $C_{24}H_{18}O_4N_2$ requires C, 72·35; H, 4·55; N, 7·0%).

1 : 4-*Dihydroxy-2-methylnaphthalenebisphenylurethane* formed colourless needles (from glacial acetic acid), m. p. 238° (Found : C, 72·6; H, 5·1; N, 6·6. $C_{25}H_{20}O_4N_2$ requires C, 72·8; H, 4·9; N, 6·8%).

1 : 4 : 5-*Trihydroxynaphthalenetrisphenylurethane* separated from aqueous dioxan in small colourless crystals, m. p. 298° (Found : C, 71·1; H, 4·2; N, 7·8. $C_{31}H_{23}O_6N_3$ requires C, 69·8; H, 4·35; N, 7·9%).

2-(p-*Dimethylaminoanilino*)-1 : 4-*naphthaquinone.*—A solution of (VI; R = H) (160 mg.) and p-nitrosodimethylaniline (150 mg.) in methanol (3 c.c.) was refluxed for 30 minutes, by which time a large mass of crystals had separated. Crystallisation from light petroleum (b. p. 100—120°) afforded small purple-brown needles, m. p. 203° (decomp.) (250 mg.) (Found : C, 74·3; H, 5·2; N, 9·6. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). Identical material was obtained by heating 1 : 4-dihydroxynaphthalene with p-nitrosodimethylaniline, or 1 : 4-naphthaquinone with p-aminodimethylaniline, in alcohol. The *amino-quinone* formed a red solution in concentrated sulphuric acid, and gave a royal-blue colour in alcoholic sodium hydroxide. Hydrolysis with 50% sulphuric acid yielded 2-hydroxy-1 : 4-naphthaquinone, yellow needles (from aqueous alcohol), m. p. and mixed m. p. 192—194° (decomp.) (acetate, m. p. and mixed m. p. 128°).

A solution of 1 : 4-dihydroxynaphthalene (or the corresponding diketone) (0·8 g.) and p-nitrosodimethylaniline (0·75 g.) in alcohol (25 c.c.) was raised to the boil. When the reaction had subsided the solution was cooled and poured into dilute sulphuric acid. The precipitate which formed was collected, yielding, after steam-distillation, yellow needles, m. p. and mixed m. p. with 1 : 4-naphthaquinone, 125° (0·7 g.). Addition of dimethylaniline and aqueous potassium dichromate to the acid filtrate gave the deep-green colour of Bindschedler's green. When 2-methyl-1 : 4-dihydroxynaphthalene (or the diketone) was heated with p-nitrosodimethylaniline in boiling alcohol for 1 hour dark crystals separated on cooling. Recrystallisation from water yielded pale yellow needles of 2-methyl-1 : 4-naphthaquinone, m. p. 106°.

Absorption Spectra.—The ultra-violet absorption spectra were determined in alcohol. As the quinone dichlorides react with alcohol the curves were plotted in sections as rapidly as possible. The absorption was read backwards from 400 to 290 mμ., after which the region 400—450 mμ., was examined giving a new curve owing to formation of chloroquinone (dotted line in the Figs.).

Part of this work was carried out in the Eidg. Techn. Hochschule, Zürich, and I am grateful to Prof. Dr. H. E. Fierz-David for the facilities placed at my disposal. I also thank the Carnegie Trust for the Universities of Scotland for a Travelling Grant, Dr. C. Daglish for the ultra-violet absorption curves, and Dr. W. C. Price for most of the infra-red data and their interpretation. Analyses, other than for active hydrogen, were carried out by Miss M. A. B. Davie.

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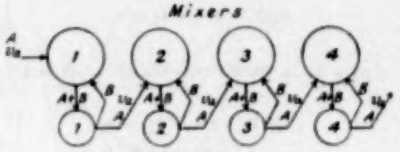
353. *The Separation of Mixtures by Continuous Extraction Processes. Part II. The Continuous Step-wise Extraction of a Fixed Quantity of a Mixture of Solutes.*

By John D. A. Johnson.

The theoretical behaviour of a solute introduced all at once into the first of a series of vessels containing two immiscible solvents so arranged that one solvent passes along the system continuously is considered. It is shown that the solute moves in the form of a wave of gradually diminishing amplitude, the speed being determined, other things being constant, by the distribution coefficient of the solute between the two liquid phases. The extent to which two or more solutes might be expected to be separated is deduced, and this method of separation of the components of mixtures is compared with the continuous counter-current process recorded in Part I.

In Part I (*J.*, 1950, 1068) the mechanism of the separation of solutes subjected to distribution between two liquids flowing in counter-current has been considered. The present communication deals with the behaviour of solutes distributed between two solvents in a series of vessels through which, however, only one of the liquids passes continuously. The principle of the process is illustrated in Fig. 1. The vessels are, for simplicity, supposed to be of equal

Fig. 1.



A = *moving solvent*. B = "*static*" *solvent*.

volume, although this is not essential; each vessel contains the same volume of "static" solvent phase, although this too is not a necessary feature. Moving solvent enters the first vessel and, after mixing with the static solvent, passes to a separator, whence the static phase passes back to the same vessel and the moving solvent proceeds to the next one in the series. It is assumed that each of the solvent phases is mutually saturated with the other before use, so there are no volume changes on mixing.

If a solute is placed in the first vessel after each of the vessels has acquired its quota of moving solvent, it will become distributed through the system in a manner which can be readily calculated. The problem is akin to that of a partition chromatogram column, which Martin and Synge (*Biochem. J.*, 1941, **35**, 1358) have treated as made up of a series of "theoretical plates" on which a degree of equilibration is achieved. They further showed that, with the ordinary rates at which the solvent moves through the column, diffusion plays only a negligible rôle. The faster the solvent moves the less the complicating effect of diffusion, but the less likely also that distribution equilibrium will be attained, since diffusion and the passage of solute from one phase to another both depend on the kinetic behaviour of the solute. In the system now being considered diffusion plays no part, since the solute can pass from one vessel to the next only in its solvent vehicle. Consequently, if desired, the rate at which the solute is passed from vessel to vessel can be made so low that there can be no doubt whatever about the essential equilibration of the contents of each vessel.

The chief feature of the process now being described is that it can deal with small quantities of material in very dilute solution, or with larger quantities in much more concentrated solution. Moreover, there is no upper limit to the size or number of vessels. It is shown below that with extended systems the behaviour is strictly analogous to that of perfectly operated partition-chromatogram columns, and that solutes can be separated as precisely as in the latter.

The symbols used in this communication have the following significance:

V = volume of each mixing vessel,
v = volume of "static" solvent present in each vessel,
$p_1, p_2 \ldots p_n$ = concentration of solute in moving solvent in vessel 1, 2, 3 .... n,
$q_1, q_2 \ldots q_n$ = concentration of solute in static solvent in vessel 1, 2, 3 .... n,
k = distribution coefficient of the solute = p/q,
x = amount of solute introduced into the system, and
v_a = feed rate of the moving solvent.

The solutes are considered to behave ideally, *i.e.*, k is assumed to be independent of concentration.

At any time, t, the amount of solute remaining in the *first vessel* is given by

$$(V - v)p_1 + vq_1 = (V - v)p_1 + vp_1/k = p_1(V - v + v/k) = x - \int_0^t v_a p_1 \mathrm{d}t$$

Differentiating, we have

$$(V - v + v/k)\mathrm{d}p_1/\mathrm{d}t = -v_a p_1$$

and since initially

$$p_1(V - v + v/k) = x$$

the general solution is

$$p_1 = kx \cdot \mathrm{e}^{-kv_a t/[kV + v(1-k)]}/[kV + v(1-k)] \quad \ldots\ldots \quad (1a)$$

Or, writing

$$k/[kV + v(1-k)] = b$$

we have

$$p_1 = kx \cdot \mathrm{e}^{-v_a b t} \quad \ldots\ldots \quad (1b)$$

In the *second vessel* at time t the following relation holds:

$$-\int_0^t v_a p_2 \mathrm{d}t + \int_0^t v_a p_1 \mathrm{d}t = (V - v)p_2 + vp_2/k$$

whence

$$-v_a p_2 + v_a p_1 = (V - v + v/k)\mathrm{d}p_2/\mathrm{d}t$$

Introducing the value of p_1 given in (1) it can be shown that:

$$p_2 = v_a b^2 x t \cdot \mathrm{e}^{-v_a b t} \quad \ldots\ldots \quad (2)$$

Similarly for *the third and the fourth vessel* the concentrations in the moving solvents are:

$$p_3 = 0{\cdot}5\, v_a^2 b^3 x t^2 \cdot \mathrm{e}^{-v_a b t} \quad \ldots\ldots \quad (3)$$

and

$$p_4 = 0{\cdot}167\, v_a^3 b^4 x t^3 \cdot \mathrm{e}^{-v_a b t} \quad \ldots\ldots \quad (4)$$

Whence, in general

$$p_n = (v_a^{n-1} b^n x t^{n-1}/\underline{|n-1}) \cdot \mathrm{e}^{-v_a b t} \quad \ldots\ldots \quad (5)$$

Choosing arbitrary values for the parameters in order to find how the concentration changes with time in the several vessels of a series, we get (for $v_a = 1$, $V = 10$, $v = 5$, $k = 1$) the data depicted in Fig. 2. This shows that the concentration maximum built up seems to travel like a wave of gradually diminishing amplitude throughout the series of vessels. It is to be noted, however, that, at any rate for the particular values of the parameters chosen, the maximum concentration in the successive vessels does not diminish rapidly, so that even with the tenth vessel, the maximum concentration is about 70% of that reached in the fifth. It should be observed that, in choosing $v = 5$ and $V = 10$, it is supposed that each vessel is half-full of static solvent, which, as will be shown presently, is not the best condition for the operation of a system.

The time at which the concentration in a given vessel is a maximum can be calculated by differentiating equation (5) and equating to zero. This gives

$$t_{(\max.)} = (n - 1)/v_A b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

from which it appears that the concentration maximum passes along at a uniform rate for a given system. As might have been expected, the greater the feed rate of moving solvent, the earlier the moment at which the maximum appears in a given vessel.

The maximum concentration in a given vessel is calculated by combining equations (5) and (6), whence

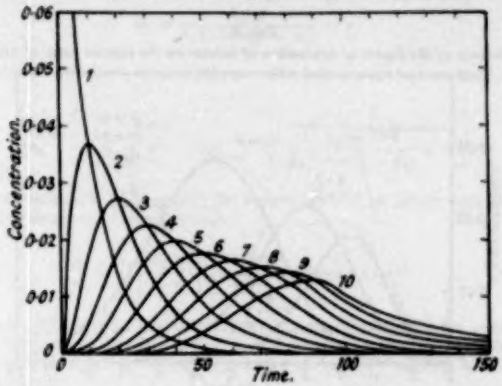
$$p_{n(\max.)} = sb(n - 1)^{n-1} \cdot e^{1-n}/\underline{|n - 1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

and the ratio of maximum concentrations in successive vessels is found by dividing this expression by one in which $(n + 1)$ replaces n. This gives

$$p_{n(\max.)}/p_{(n+1)(\max.)} = [(n - 1)/n]^{n-1} e.$$

By introducing various values of n into this expression a measure of the rate at which the " wave " dies down may be deduced; it is found by such substitutions that the decrement is

FIG. 2.



Concentration–time relation for a series of vessels for the arbitrary values: $v_A = 1$; $V = 10$; $v = 5$; $h = 1$.

surprisingly low, which indicates that the solute has a great tendency " to keep together " as it passes along an extensive system, although it must be quite clear that, theoretically, solute must be present indefinitely in all vessels from the moment it is introduced into the system. The concentration in vessels remote from that carrying the maximum is, however, negligibly small and the exact disposition of solute is deduced later.

It is clearly necessary to qualify the statement often made, in connection with partition chromatography in tubes and with paper chromatography, that an ideal solute moves in a band which (when h is constant) shows no tendency to spread. These bands must spread and in general become more diffuse the further they travel along a system. It is true that in a very extended system this effect will be almost imperceptible.

At the moment when the concentration in a given vessel reaches its maximum, such concentration is equal to that in the preceding vessel. This can be shown by observing that, when the concentration in the nth vessel reaches its maximum [equation (6)], the concentration in the $(n - 1)$th must, from (5), be

$$\begin{aligned} p_{n-1} &= (sv_A^{n-2}b^{n-1}t^{n-2}/\underline{|n - 2}) \cdot e^{-v_A bt} \\ &= sb(n - 1)^{n-1} \cdot e^{1-n}/\underline{|n - 1} \end{aligned}$$

when the appropriate value of t is introduced. This expression for p_{n-1} is identical with (7), and explains why the curves given in Fig. 2 intersect as shown. It appears, therefore, that

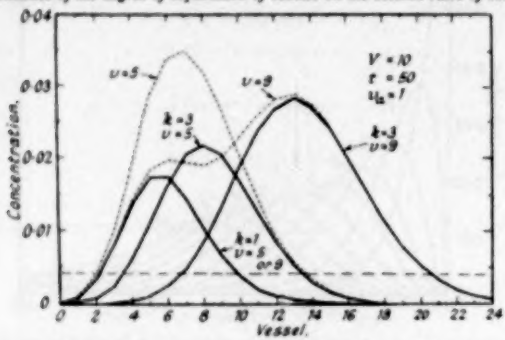
when the concentration in a vessel is higher than it is in any other vessel, it is itself already declining.

Separation of Two Solutes.—From equation (6) it is clear that the time at which the maximum concentration in a given vessel is reached depends on the distribution coefficient of the solute, the volume of the vessels, the volume of static solvent present, the flow rate of the mobile phase, and the number of the vessel in the series. For a given set-up, therefore, the time is dependent on k, indicating the possibility of separating two or more solutes. However, the *ratio* of $v : V$ is important for the efficiency of separation. To illustrate this, suppose that the volume of the vessel is 10, that v_a is 1, and that the separation of two solutes having $k = 1$ and 3, respectively, is being attempted. In one case, let the ratio of $v : V$ be 0·5, and in a second case be 0·9. The concentrations in each of the vessels of a long series at time $t = 50$, for example, can be calculated from equation (5), and Fig. 3 illustrates the result.

It is seen that when $v : V = 0{\cdot}9$ the peak concentrations of the two solutes are separated to a greater degree than when $v : V = 0{\cdot}5$. If the two solutes were of the same nature, say were both acids, the apparent total acidity of the contents of the various vessels could be represented by the sums of the separate concentrations of the two solutes, the broken lines in the Fig. 3 representing the results of such summations. With the lower ratio $v : V$ the presence of two solutes could be inferred from the slight kink in the total acidity curve, but it is evident that

FIG. 3.

Dependence of the degree of separation of solutes on the volume ratio of solvents.



little separation of the solutes would result by $t = 50$. When $v : V$ is 0·9, however, the " kink " is much more pronounced and appreciable separation of the solutes has occurred.

If v is supposed to become equal to V, equation (5) becomes

$$p_n = (xv_a^{n-1}k^n t^{n-1} \cdot e^{-kv_a t/V})/(V^n|n-1)$$

and the maximum concentration in a given vessel, obtained by differentiating this expression, is reached when

$$t_{(max.)} = V(n-1)/kv_a$$

The interpretation of this is, that when the volume of " static " solvent in each vessel approaches the volume of the vessel itself, the time at which the maximum concentration of a given solute is reached in a specified vessel is inversely proportional to the distribution coefficient of the solute. In other words, the greater the value of k, the earlier the maximum appears in a given vessel, as might have been surmised. More important, *the maximum of concentration passes along the system at a uniform rate, which is proportional to the distribution coefficient, like a gradually dying wave and, with two or more solutes, the relative distances travelled in the system by these maxima bear a simple relationship to one another, being again proportional to the distribution coefficients of the solutes.* (It should be remembered that in making these deductions the maximum concentration has been assumed to be that in the vessel which has just reached its maximum, and this has been shown to be the same as that existing in the preceding vessel at the same

moment. With an extended series of vessels the difference between the sth and $(s-1)$th vessels is so slight that the conclusions just reached become almost exact.)

In these calculations, it has been assumed that through a series of vessels, almost full of static solvent, a thin stream of moving solvent has been passed, and this approximates closely to partition-chromatogram columns in which the hold-up of the developing phase is small compared with the actual volume of the static phase and its support. It has been indicated above that when the ratio $v : V$ is low the separation of solutes is not so effective, whence it may be concluded that most efficient operation of partition-chromatogram columns requires close packing of the columns. Similarly, since paper chromatography closely resembles chromatography with such columns, swamping the paper with the developing liquid should be carefully avoided. (The strict analogue of paper chromatography is a series of vessels not quite filled with static solvent, through which the moving solvent passes, carrying the solutes along with it. The vessels are successively filled by the moving solvent. This arrangement is insensibly different from that just considered, when the ratio $v : V$ approaches unity.)

It can readily be shown that a system of many vessels is most efficient when v approaches V. Thus, from equation (6), the vessel n_1 in which the maximum of concentration of solute 1 having a distribution coefficient k_1 is to be found, is given by

$$n_1 = \frac{k_1 v_0 f}{k_1 V + v(1 - k_1)} + 1$$

and a similar relation holds for a second solute. The best separation of the two solutes will be when

$$\frac{n_1}{n_2} = \left[\frac{k_1 v_0 f}{k_1 V + v(1 - k_1)} + 1\right]\left[\frac{1}{\frac{k_2 v_0 f}{k_2 V + v(1 - k_2)} + 1}\right]$$

is a maximum or a minimum. Obviously, the separation will be better with a larger number of vessels, so the unity terms may be neglected :

$$\frac{n_1}{n_2} = \frac{k_1}{k_2}\left[\frac{k_2 + f(1 - k_2)}{k_1 + f(1 - k_1)}\right], \text{ where } f = v/V$$

Differentiating n_1/n_2 with respect to f shows no maximum or minimum for values of f between 0 and unity; and since when $f = 0$, $n_1/n_2 = 1$, and when $f = 1$, $n_1/n_2 = k_1/k_2$, the maximum separation of two solutes follows the use of volumes of " static " solvent almost equal to those of the containing vessels.

To some extent this could have been expected on general grounds, since such a method of operation of the system is equivalent to the extraction of a solute from one solvent by a large number of extremely small quantities of a second solvent.

It is important to note that pairs of solutes having $k < 1$ will move relatively slowly compared with those having $k > 1$, yet nevertheless two solutes having $k < 1$ can be separated just as efficiently as two solutes having $k > 1$ provided that the ratio of their distribution coefficients is sufficiently large. However, it would in such a case be desirable practically to reverse the rôle of the solvents, the distribution coefficients applicable being then the inverse of the conventional values, so that a more speedy passage of the solutes along the system occurs with just as efficient a separation.

Shape of the Curve connecting Number-of-vessel with the Concentration of its Contents.—So far, in considering the separation of solutes we have been concerned mainly with the extent to which the peak concentrations of the solutes are separated from one another. It is clear from Fig. 3 that appreciable concentrations of solute exist in the vessels on either side of that in which the maximum concentration occurs, and that two solutes may exist together in appreciable, and more or less equal, concentrations in the vessels between those carrying their maxima. It is, therefore, of interest and importance to know something of the shape of the curve connecting concentration with the number-of-vessel, since the imperfection of separation of two solutes depends on the extent to which the curves for the solutes are superimposed. The common area under both curves is a measure of this imperfection and it should be made as small as possible.

Furthermore, we have supposed that the degree of separation of two solutes is directly connected with the degree of separation of the peaks of concentration and this will only be

justified if it can be shown that the shape of the "concentration waves" is unconnected with the value of h.

The ratio of the maximum concentration p_n to the concentrations in the vessels in front of and behind the vessel in which the maximum has been reached can be derived for a given time as follows. For the vessel situated one in advance of the vessel having the maximum concentration, the concentration is:

$$p_{n+1} = v_d^n b^{n+1} t^n \cdot e^{-v_d bt}/\underline{n}$$

giving the ratio $p_{n+1}/p_n = v_d bt/n$ $= (n-1)/n$ [from equation (6)]

Similarly, $p_{n+2}/p_n = v_d^2 b^2 t^2/[(n+1)n]$ $= (n-1)^2/[n(n+1)]$

and $p_{n+3}/p_n = v_d^3 b^3 t^3/[n(n+1)(n+2)]$ $= (n-1)^3/[n(n+1)(n+2)]$

. . . . . .

$$p_{n-1}/p_n = (n-1)/v_d bt = 1$$

$$p_{n-2}/p_n = [(n-1)(n-2)]/v_d^2 b^2 t^2 = (n-2)/(n-1)$$

$$p_{n-3}/p_n = [(n-1)(n-2)(n-3)]/v_d^3 b^3 t^3 = [(n-2)(n-3)]/(n-1)^2$$

or, generally, $p_{n+r}/p_n = (n-1)^r/[n(n+1)(n+2)\ldots\ldots(n+r-1)]$ for the rth vessel in front of that in which the maximum concentration occurs

and $p_{n-r-1}/p_n = [(n-2)(n-3)\ldots\ldots(n-r+1)]/(n-1)^r$ for the $(r+1)$th vessel behind that in which the maximum concentration ocurs. (8)

The concentrations are, therefore, not quite symmetrically distributed about the *two* vessels in which the concentrations are equal. In general, the concentration in the $(n+r)$th vessel is slightly higher than it is in the $[n-(r+1)]$th vessel, but with extended systems the curves become more and more symmetrical as time proceeds. The general position is shown in Fig. 3.

It may be supposed that in partition chromatography, including paper chromatography, a similar state of affairs exists. If a given reagent can detect a solute only when its concentration is above a critical value indicated by the broken horizontal line in Fig. 3, the advanced edge of the solute spot detected will appear less sharp than the retreating edge because for the latter the approach to the region of non-detectability is more abrupt. This might account for "diffuse heads" in paper chromatography, while variations in h might explain "tailing" (as several workers have suggested). A variation in h would also tend to produce a sharpened front. With very extended systems such as paper chromatograms, however, the difference between the two sides of the peak is very slight and another explanation may have to be sought. It is also worth note that, since in paper chromatography one is dealing with minute amounts of material—altogether often only a few times the minimum detectable quantities—it may be unwise to rely on measurements of areas of spots for quantitative work; for at points not very remote from the centre of the spot there may be undetectable quantities of the solute, inconsiderable in themselves but forming, nevertheless, a fair proportion of the total amount of solute present.

The most important feature to be observed from equation (8) is that the relative concentrations of a solute present in a specified vessel and that carrying the peak concentration depend only on the number of the latter vessel in the system, whence it follows that the distributions of all solutes about the vessel containing the peak concentration are the same. This means that the shapes of the curves connecting concentration with number-of-vessel depend only on the value of n. In the table are given the concentrations, in all vessels relative to the maximum, for selected values of n (in which vessel the maximum occurs), and these data apply whether the system is being operated under the optimum conditions or not. ***Since it has already been shown that maximum separation of peaks occurs when*** $v = V$, ***it follows that there is less overlap of the concentration waves when this condition applies and that, indeed, it is a condition for most efficient operation of the system.***

Vessel.	$n = 20$.	$n = 40$.	$n = 60$.	$n = 80$.	$n = 100$.
$n - 34$	—	—	—	—	0·001
$n - 33$	—	—	—	—	0·002
$n - 32$	—	—	—	—	0·003
$n - 31$	—	—	—	0·001	0·005
$n - 30$	—	—	—	0·002	0·007
$n - 29$	—	—	—	0·003	0·010
$n - 28$	—	—	—	0·004	0·014
$n - 27$	—	—	0·001	0·006	0·020
$n - 26$	—	—	0·002	0·009	0·026
$n - 25$	—	—	0·003	0·014	0·036
$n - 24$	—	—	0·005	0·020	0·047
$n - 23$	—	—	0·007	0·028	0·061
$n - 22$	—	—	0·011	0·039	0·079
$n - 21$	—	0·001	0·017	0·053	0·100
$n - 20$	—	0·003	0·026	0·071	0·126
$n - 19$	—	0·005	0·039	0·093	0·158
$n - 18$	—	0·009	0·056	0·121	0·191
$n - 17$	—	0·016	0·077	0·155	0·230
$n - 16$	—	0·027	0·106	0·194	0·275
$n - 15$	0·001	0·045	0·142	0·240	0·325
$n - 14$	0·002	0·070	0·186	0·292	0·379
$n - 13$	0·005	0·105	0·238	0·350	0·436
$n - 12$	0·011	0·151	0·299	0·412	0·498
$n - 11$	0·026	0·211	0·368	0·480	0·559
$n - 10$	0·055	0·283	0·444	0·549	0·623
$n - 9$	0·104	0·368	0·524	0·620	0·686
$n - 8$	0·179	0·463	0·606	0·692	0·747
$n - 7$	0·284	0·564	0·685	0·759	0·803
$n - 6$	0·414	0·667	0·767	0·822	0·856
$n - 5$	0·562	0·765	0·838	0·878	0·901
$n - 4$	0·712	0·853	0·900	0·926	0·940
$n - 3$	0·847	0·924	0·948	0·962	0·970
$n - 2$	0·947	0·974	0·983	0·987	0·990
$n - 1$	1·000	1·000	1·000	1·000	1·000

Vessel.	$n = 20$.	$n = 40$.	$n = 60$.	$n = 80$.	$n = 100$.
n	1·000	1·000	1·000	1·000	1·000
$n + 1$	0·950	0·975	0·983	0·987	0·990
$n + 2$	0·880	0·927	0·951	0·962	0·970
$n + 3$	0·743	0·861	0·905	0·927	0·940
$n + 4$	0·613	0·780	0·846	0·881	0·903
$n + 5$	0·486	0·691	0·780	0·828	0·858
$n + 6$	0·379	0·598	0·708	0·770	0·809
$n + 7$	0·270	0·508	0·632	0·707	0·755
$n + 8$	0·190	0·422	0·557	0·642	0·698
$n + 9$	0·129	0·342	0·482	0·575	0·640
$n + 10$	0·084	0·273	0·412	0·510	0·580
$n + 11$	0·053	0·212	0·348	0·447	0·522
$n + 12$	0·032	0·163	0·288	0·389	0·466
$n + 13$	0·019	0·122	0·236	0·333	0·412
$n + 14$	0·011	0·090	0·191	0·283	0·360
$n + 15$	0·006	0·065	0·152	0·238	0·312
$n + 16$	0·003	0·046	0·120	0·198	0·268
$n + 17$	0·001	0·032	0·093	0·162	0·228
$n + 18$	—	0·022	0·077	0·132	0·193
$n + 19$	—	0·015	0·058	0·106	0·162
$n + 20$	—	0·010	0·043	0·085	0·134
$n + 21$	—	0·006	0·032	0·067	0·111
$n + 22$	—	0·004	0·023	0·052	0·091
$n + 23$	—	0·002	0·017	0·040	0·073
$n + 24$	—	0·001	0·012	0·031	0·059
$n + 25$	—	—	0·008	0·024	0·047
$n + 26$	—	—	0·006	0·018	0·037
$n + 27$	—	—	0·004	0·013	0·029
$n + 28$	—	—	0·002	0·010	0·023
$n + 29$	—	—	0·001	0·007	0·018
$n + 30$	—	—	—	0·005	0·014
$n + 31$	—	—	—	0·004	0·010
$n + 32$	—	—	—	0·003	0·008
$n + 33$	—	—	—	0·002	0·006
$n + 34$	—	—	—	0·001	0·004
$n + 35$	—	—	—	—	0·003
$n + 36$	—	—	—	—	0·002
$n + 37$	—	—	—	—	0·001

Degree of Separation of Solutes.—A system of the type now being considered could be operated in two ways, analogous to two of the procedures used in chromatography in columns, whether of the adsorption, ion-exchange, or partition types. On the one hand, a mixture of solutes could be introduced into an extended system of vessels and the solutes isolated from the emergent liquid phase. Naturally, if water were the moving phase the solute appearing first in quantity would be that with the highest value of k whatever the amount of this solute compared with that of others. It is true that if this solute were present in very small amount, it might be contaminated with large amounts of solutes of lower distribution coefficient present in predominant quantities, but some concentration of the former solute would nevertheless be effected if the effluent liquid were cut at the appropriate point in the process.

The second method of operating the system would be to introduce the mobile phase until the various solutes were distributed throughout the system and then, after having examined the contents of each vessel, to work up the contents of appropriate vessels on the basis of this examination. There are advantages and disadvantages in both methods, but the method of choice is the former since it is necessary to keep a watch only on the effluent liquid phase; and, most important of all, such a system is considerably more efficient than the other, because full advantage is taken of all the vessels in the system, whereas in the second method some of the solutes will undergo separation by relatively few vessels.

Some idea of the separations to be expected using the second method may be gained from the data in the Table. If the system comprises about 140 vessels and the process has been conducted for such a time that the peak concentration of a solute having the highest value of k_1 is in vessels 99 and 100, then the peak concentration of a second solute having $k_2 = 0{\cdot}8k_1$ will be in vessels 79 and 80. If, furthermore, we assume (and this will be the general assumption throughout this paper in assessing efficiency of separation) that the solutes are present in equal amounts in the system, then vessels 80—100 contain mixtures of various amounts of these two solutes. Thus concentration, in the mobile phase, of the solute of lower value of k in vessel 89 is 0·575 of the peak value, and the concentration of the other solute is 0·589 of its peak value in the same solvent. There is thus an extensive overlap of the two solutes, even with a system

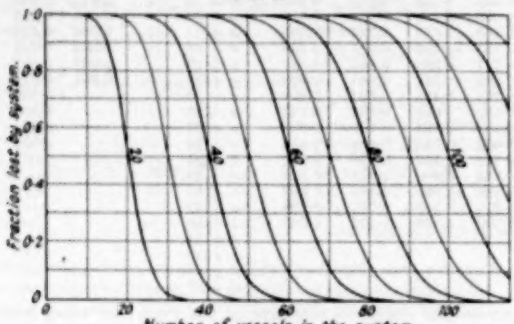
comprising 140 vessels. By working up the contents of vessels 90—140 for one solute and the contents of the remaining vessels for the other, the two substances could be obtained approximately 86% pure. Even this is quite good when the closeness of the distribution coefficients is considered. (Operating according to the first method this purity is achieved with 95 vessels.)

The actual point at which to divide the contents of the system is not easily decided when the two solutes are present in unequal amounts and, for this and other reasons already given, this method of operation is not recommended. Attention will, therefore, be directed to the alternative procedure.

Theoretically, even from the outset, *all* solutes emerge from the system, but at different rates. Only after some time will the concentration of the solute of highest distribution coefficient become detectable. Thereafter it will rise to a maximum and then fall to zero after infinite time. The problems to be solved include the point at which to make the "cut," and the minimum number of vessels necessary to permit reasonable separation of solutes.

The rate of emergence of a solute is $v_a p_y$ where p_y is its concentration in the moving solvent

FIG. 4.



(*Values of $v_a bt$ are given on the curves.*)

in the last vessel N of the series. The total amount Q which has left the vessel by time t is given by

$$Q = \int_0^t v_a p_y \mathrm{d}t$$

which, by equation (5) becomes

$$Q = [v_a^N b^N x/\underline{(N-1)}]\int_0^t t^{N-1} e^{-v_a bt} . \mathrm{d}t$$

The integral can be obtained by reduction and, denoting the fraction of the solute introduced into the system which has left by time t by F, we get

$$F = \left[1 - \frac{e^{v_a bt} \text{ expanded to } N \text{ terms}}{e^{v_a bt} \text{ to an infinite number of terms}}\right] \quad . \quad . \quad . \quad . \quad . \quad (9)$$

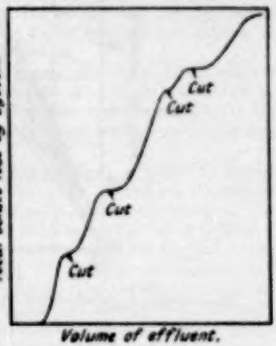
Evaluation of this expression is tedious and in Fig. 4 the only curves which have been calculated are those for $v_a bt = 20$, 40, 60, 80, and 100. Fortunately it is simple to interpolate values for F and the remaining curves in Fig. 4 have been derived in this way.

For a given system, the various amounts F_1, F_2 . . . . . of solutes having distribution coefficients k_1, k_2 . . . . . which have left the system by time t could be calculated from equation (9), but it is simpler to use Fig. 4 especially if the ratio of these amounts is sought. We shall suppose, in the first place, that the system is operated in the most efficient manner, whence the exponents in equation (9) reduce to $kv_a t/V$, in which the only variable is the distribution coefficient if we are considering a given time. Consequently, the various relations in Fig. 4 can be regarded as referring to solutes having values of k determined by the values of $v_a bt =$

$kv_s t/V$ recorded on the curves. Thus if we wish to consider the fractions of two solutes having $k = 1{\cdot}0$ and $2{\cdot}0$ which have emerged from a system of 40 vessels we can refer to curves for $kv_s t/V = 20$ and 40, or 25 and 50, and so on, realising that the precise pair which must be chosen to arrive at the solution of our problem will be completely determined by the values of v_s, V, and t. To illustrate the use of Fig. 4, suppose that two solutes having $k = 2$ and 3 are introduced in equal amounts into a system of 50 vessels (each having a volume of 10 units) and that the feed rate of the moving solvent is 1 unit. The fractions of the two solutes which would have left the system by $t = 200$ would be (since $kv_s t/V = 40$ and 60) 0·070 and 0·915 respectively. Thus, if these were the only solutes present, the material which would have emerged by this time would be $0{\cdot}915 \times 100/(0{\cdot}915 + 0{\cdot}070) = 92{\cdot}9\%$ pure. If the cut were made at this moment and the passage of mobile phase continued, the second solute could be isolated $\dfrac{(1{\cdot}000 - 0{\cdot}070) \times 100}{(1{\cdot}000 - 0{\cdot}070) + (1{\cdot}000 - 0{\cdot}915)} = 91{\cdot}6\%$ pure. If on the other hand the cut were made much earlier or later, the two components would be isolated in widely different purities. Thus if t were 300, $kv_s t/V$ would be 60 and 90, giving, as the fractions eliminated, 0·915 and 1·00; the two materials then being obtainable 52·3% and almost 100% pure respectively. The amount of the substance having the latter purity would be, however, only 8·5% of that introduced into the system. If we define as the best degree of separation, that which leads to the isolation of both solutes in the same degree of purity, then the cut should be made at such a time that the amount of the one solute which has left the system is equal to the amount of the other which remains in the system. This can be determined by examination of the appropriate curves in Fig. 4, and it will be seen that the curves corresponding to $t = 200$ (giving $kv_s t/V = 40$ and 60) are not far from the ideal for the example given. In practice, of course, the precise moment for the cut can be ascertained in two ways. On the one hand the actual total amount of all solutes which has left the system can be plotted against time and the cut made when the curve takes the trend which indicates that a second solute is emerging (Fig. 5), or a chemical or physical property of the effluent can be plotted against volume (or time, if the feed rate of the mobile phase is steady) and the cut made appropriately. The greatest uncertainty will be for solutes having similar k values, or when the amount of one solute is considerably greater than that of another.

FIG. 5.

General pattern of discharge diagram.

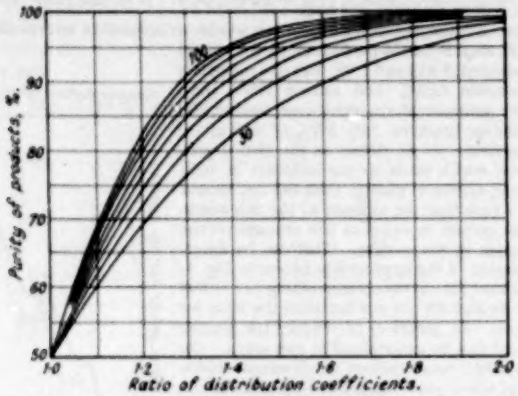


We shall next consider the number of vessels required to achieve good separation. Martin and Synge (*loc. cit.*) have given some idea of the theoretical-plate efficiency of the columns studied by them, and Stein and Moore (*J. Biol. Chem.*, 1948, **176**, 337) have stated that their columns have an efficiency equivalent to 2000 theoretical plates. The sharp separation of many amino-acids from one another in paper chromatography is eloquent testimony to the theoretical-plate efficiency of this simple technique. To gain some idea of the value of the system now being considered, let us suppose that it comprises 100 vessels. Fig. 4 shows that curves for $v_s bt = kv_s t/V = 90$ and 110 will be suitable pairs for consideration since both solutes would emerge equally pure. The actual purity would be 84·3%. Such a purity would refer to solutes whose distribution coefficients were in the ratio of 110 : 90 = 1·22. Similarly, curves for 80 and 122 form a suitable pair, corresponding to a distribution coefficient ratio of 1·525 and a purity of 98·4%. By proceeding in this way, the relation between distribution-coefficient ratio and purity can be calculated for a system of 100 vessels, and similar relations for smaller systems can readily be deduced. Fig. 6 illustrates the results of such computations and may be used to design apparatus for separating mixtures of solutes.

As might have been expected, the longer the system, the better the separation, and with 100 vessels the performance should be very good indeed. Thus solutes having a distribution coefficient ratio of 1·3 should be obtained over 90% pure and, if the ratio is 1·6, the purity would be over 99%. With systems as short as 30 vessels products of 90% purity would result if the k ratio were 1·6. This is near the lower limit of usefulness and it can be assumed that for the effective separation of solute mixtures, at least 50 vessels should be used and 50—100 would probably satisfy most demands. It is to be appreciated of course that if the desire is to

isolate pure solutes, the efficiency of this operation being a secondary consideration, the cut can be made at an earlier point than usual (which will give the first solute in a purer state), a second fraction of solutes in approximately equal amounts can then be taken and, after the second cut, the second solute can be isolated in a high degree of purity from the third fraction of emergent solvent phase. The second fraction can then be re-cycled through the system. Alternatively, the cut can be made in the usual way and the less pure fractions re-cycled separately. Thus for a 30-vessel system and solutes having a k ratio of 1·6, the products will be 90% pure after the first run. If these are now re-cycled and the cut made at the same time as before the products would be $90 \times 100/91 = 99\%$ pure. Operating in this way is, of course, tantamount to having a longer system. Re-passage of solute through n vessels can give a purer product than is obtainable with $2n$ vessels.

FIG. 6.



The numbers of vessels in the series are 30, 40, 50, 60, 70, 80, 90, *and* 100 *for the curves ranging from the lowest to the topmost, respectively.*

In the discussion just presented it has been assumed that the system has been operated in the most efficient manner, that is, that the moving solvent has comprised only a vanishingly small proportion of the contents of each vessel. In practice, of course, it would usually be difficult to operate the system unless the moving phase occupied at least a small fraction of the volume of each vessel, because the separators must be capable of dealing effectively and continuously with the mixed solvent phases. If the separators were continuous centrifuges, they could almost certainly deal with a solvent volume ratio of 9 : 1 which, however, is probably the lowest value to which it should fall. Using finite volumes of moving solvent causes concentration waves for different solutes to crowd together somewhat and the extent to which this lowers efficiency can be evaluated as follows.

Denoting the appropriate values of $kv_s t/[kV + v(1 - k)]$ (*i.e.*, $v_s kt$) derived from Fig. 4 for, say, 100 vessels by P_1 and P_2, so that

$$k_1 v_s t/[k_1 V + v(1 - k_1)] = P_1 \text{ and } k_2 v_s t/[k_2 V + v(1 - k_2)] = P_2$$

it can readily be shown that

$$\frac{k_1}{k_2} = \frac{P_1}{P_2} + \frac{k_1(P_1 - P_2)[V - v]}{P_2 v} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

In discussing the most efficient systems, v was supposed equal to V, whence this expression reduced to $k_1/k_2 = P_1/P_2$ and this was the basis of the deductions given earlier. It is now seen that in practice the ratio k_1/k_2 corresponding to a certain purity which may be ascertained from Fig. 4 is actually dependent on k_1. For given values of P_1 and P_2 ($P_1 > P_2$), the ratio k_1/k_2 is greater than P_1/P_2 if $v \neq V$. The greater the value of k_1, the greater the ratio k_1/k_2. Thus the purity corresponds to P_1 and P_2 when the ratio of distribution coefficients is higher than

indicated in Fig. 6, and the effect is most noticeable with high values of k. Thus, taking $P_1 = 113{\cdot}1$ and $P_2 = 87{\cdot}5$ from Fig. 4 for a 100-vessel system, and $v = 0{\cdot}9V$, we get

$$k_1/k_2 = 1{\cdot}292 + 0{\cdot}0325k_1$$

If k_1 is 2, the ratio is 1·357; if k_1 is 10, it is 1·617.

The effect is also more noticeable if P_1 and P_2 correspond to higher purities. Thus it is most desirable to operate with each vessel filled as much as possible with the static phase. This will throw a strain on gravity-type separators such as those described in Part I, since for each volume of mobile phase passing through them there must be at least ten volumes of mixed solvents. Centrifugal separators would be able to deal adequately with this problem and an operation need not last more than a few hours.

The time and the volume of mobile solvent phase taken for a separation can be ascertained from Fig. 4. If the time is defined as that required for the elimination of 99% of the last solute to be discharged from the system, the value of P which corresponds to the number of vessels used can be read off. Thus if the system comprise 100 vessels, P is approximately 123, whence $v_g t$ can be calculated from the expression $P = v_g bt$ if the lowest distribution coefficient of the mixture of solutes is known approximately. If $v = 0{\cdot}9$, $V = 9$, and $k_{min.} = 0{\cdot}5$, $v_g t$ becomes 2337. The rate of flow of the mobile phase being known, t can be calculated. The expression $v_g t$ is the total volume of the mobile phase used and it amounts, in the example just quoted, to 2·337 times the total volume of the 100 vessels, which is not excessive.

Comparison of the Continuous Counter-current and Continuous Step-wise Techniques of Separation of Solutes.—In the continuous counter-current method of separating two solutes by distribution between solvents, the solutes move in opposite directions but the transfer is not direct. Each part of solute stands a considerable chance of being temporarily transported in a direction opposite to that of its general movement.

The process is not unlike the behaviour of a solute diffusing from a point of higher concentration which itself possesses movement of translation. This to-and-fro movement improves the solute separation so that the system is superior to a system operating on the continuous step-wise plan. By comparing Fig. 6 of this communication with Fig. 9 of Part I, it will be seen that a system of 35 vessels arranged in counter-current fashion is as good as one of 100 vessels in which the moving solvent flows step-wise. The relative advantages and disadvantages of the two systems can be summarised as follows. The continuous counter-current arrangement requires a less extended system, and two solutes emerge simultaneously from opposite ends; it does not involve the difficulties of separating the two solvent phases inherent in operating the step-wise system under conditions approximating to the optimum. On the contrary, to take full advantage of the counter-current method, the flow rates of the two solvents must be very closely controlled.

Experiments describing the application of the continuous step-wise process will be described later.

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354. *First-order Asymmetric Transformation arising from Solvation.*

By J. Glazer, Margaret M. Harris, and E. E. Turner.

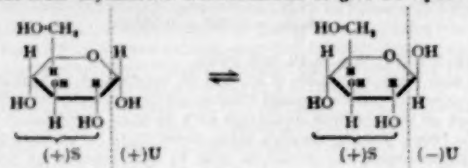
It is shown that first-order asymmetric transformation can occur as a result of solvation between an optically unstable compound and an optically active, optically stable solvent. (Unless solvation extends to solid phases, second-order asymmetric transformation cannot occur.)

The potential optical activity of 8-nitro-*N*-benzenesulphonyl-*N*-(2-hydroxyethyl)-1-naphthylamine has been demonstrated by its optical activation in ethyl (+)-tartrate.

A substance, the molecule of which contains both a centre of stable optical activity [(+)S] and one of unstable optical activity [(+)U or (−)U], when dissolved in a suitable solvent, may be represented as an equilibrium between two diastereoisomerides:

$$(+)S(+)U \rightleftharpoons (+)S(-)U$$

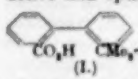
An excellent example of such a substance is the mutarotating sugar glucose, which in aqueous solution undergoes first-order asymmetric transformation to give an equilibrium mixture of



α- and β-glucose [in aqueous solution there is not more than 0·02% of open-chain glucose (Cantor and Peniston, *J. Amer. Chem. Soc.*, 1940, 62, 2113)]. The substance may be a salt, *e.g.*, of an alkaloid with an optically labile acid; it must then be dissolved in a solvent such as chloroform in which the diastereoisomeric salts exist as such, and not in one such as water in which ionisation or solvolysis predominates. Solvation of one or both of the diastereoisomers would not prevent the establishment of an equilibrium between them, provided that other circumstances were favourable.

During the last ten years we have given much consideration to the possibility of detecting a stereochemical equilibrium which is of the general type outlined but arises from the union such as has often been shown to exist between solute and solvent. There would be no formal covalent or ionic bond between S and U, but a looser association such as might be provided by the hydrogen bridge. The ideal experiment, as we conceived it, was to dissolve an optically labile substance in an optically stable solvent with which it might be expected to associate and to look for the mutarotation which should accompany equilibration (if the optical instability and the extent of disturbance of the equilibrium were in the observable range).

Since carboxylic acids are known normally to form dimeric molecules, it is probable that analogous inter-acid complexes are formed between two acids, so that an obvious type of experiment would be to dissolve an optically unstable acid (U) in an optically stable, resolved acid as solvent (S). So far this has not been found practicable, and we have had recourse to the less satisfactory experimental procedure of dissolving in chloroform two acids, one optically active and optically stable, the other racemic and optically labile. As substance (−)S we selected (−)-*sec.*-octyl hydrogen phthalate and as substance U racemic 2′-(2″-hydroxy-2″-propyl)diphenyl-2-carboxylic acid (I), previous examination (Jamison and Turner, *J.*, 1942, 437) of which had shown it to possess a manageable degree of configurational stability. A mixture of the two acids in chloroform solution did in fact exhibit slow mutarotation well outside experimental error. Moreover, the solubility of the acids appeared to increase with time in contact with the solvent, an indication that some definite change was in progress before rotational examination was possible (cf. Hudson and Janovsky, *J. Amer. Chem. Soc.*, 1917, 39, 1013). It thus appeared that first-order asymmetric transformation was being witnessed. On attempting to nullify the effect of (−)S by adding (+)-*sec.*-octyl hydrogen phthalate, an inconclusive result was obtained, for although the total rotation changed at once, it then remained constant. Earlier experience had shown that the mutarotation which was observed was almost certainly not caused by lactonisation of the unstable acid, all attempts to obtain an active lactone from an active acid having failed.



(I.)

***N*-Benzoyl-2 : 4-dimethyldiphenylamine-2′-carboxylic acid, an acid of very low configurational stability and known (Jamison and Turner, *J.*, 1938, 1646) to give a very characteristic " addition curve " with (+)-nor-ψ-ephedrine in chloroform solution, was selected as suitable material (U) for observing any change in rotation accompanying its addition, in increasing quantities, to a chloroform solution of (−)-*sec.*-octyl hydrogen phthalate. Such a solution had α −5·88° (l = 2). Addition of 0·16, 0·32, and 0·48 equivalent of the unstable acid caused an immediate change in rotation of the solution to −6·11°, −6·33°, and −6·48° respectively. Solubility limits prevented further additions, but one interpretation of the results obtained would be that hydrogen-bridged diastereoisomerides are here behaving similarly to salt-diastereoisomerides.**

Failing, for the moment, a sufficient supply of an optically stable, active liquid acid with good solvent properties, attention was turned to other types of optically active solvent. The experimental difficulties in attempting to observe first-order asymmetric transformations in such a solvent are considerable. First, very few such solvents are available in any quantity.

Secondly, any mutarotation observed in them is likely to be small in comparison with the rotation of the solvent, so that small differences have to be examined very critically; the temperature effect on the pure solvent is often very large and needs close control. Thirdly, observation of mutarotation of a solution of an originally racemic substance in an optically active solvent could not safely be referred to optical activation in absence of evidence that total precipitation of the solute gave an optically active product. Also, if an equilibrium is under investigation, such precipitation must be rapidly achieved.

An optically active hydroxylic solvent which is obtainable in some quantity is ethyl (+)-tartrate, particularly suitable for our purpose since, as has long been known, it possesses powerful solvating properties. Moreover, it is readily soluble in water, in which most of the other experimental material is insoluble, thus permitting rapid removal of solvent and "freezing" of the equilibria in the erstwhile racemic solutes, and subsequent polarimetric examination of the solid material obtained.

The first experiments with ethyl (+)-tartrate were conducted using two acids which had previously been shown to possess the desired order of configurational stability (Jamison and Turner, *J.*, 1940, 264). *N*-Benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylic acid could not be dissolved to a sufficient extent in cold ethyl (+)-tartrate, so that direct observation of mutarotation was impossible: but at about 90° a solution was readily obtained and was cooled and kept overnight. The total dissolved solid was recovered by addition of an excess of water: in chloroform solution it was lævorotatory (observed α_{5461} −0·06° 1·4 minutes after being wetted). The next day the solution was inactive. *N*-Benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylic acid was even less soluble than the chloro-methyl-acid in ethyl tartrate, but a similar general procedure led to a feebly lævorotatory acid (observed α_{5461} −0·04°, becoming zero overnight).

The acids of this series being so sparingly soluble in ethyl (+)-tartrate, the corresponding methyl esters were examined. A solution of methyl *N*-benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylate was made by shaking the finely-ground ester (5 g.) with ethyl (+)-tartrate (150 c.c.) at room temperature for 15 minutes. The suspension was filtered. Part (*A*) of the solution was placed in a temperature-controlled polarimeter tube (25°), part (*B*) at once treated with excess of water, and part (*C*) kept at 25° in a thermostat. The observed rotation of *A* changed during 18 hours from +20·51° to +20·47° ($\lambda = 5461$; $l = 2$), indicating a slight optical activation producing (−)-ester–(+)-solvent. The ester similarly obtained from *B* had $[\alpha]_{5461}^{25}$ −2·8° in AnalaR chloroform solution (*c*, 0·900) 2·4 minutes after being wetted with solvent. Racemisation followed first-order kinetics. Solution *C* was treated with water at the time that solution *A* attained constant rotation. The water-precipitated ester had $[\alpha]_{5461}^{25}$ −3·5° in AnalaR chloroform solution (*c*, 3·100) 3 minutes after being wetted with solvent. Racemisation followed first-order kinetics (period of half-racemisation, 6 minutes). From this experiment it was concluded that optical activation of the racemic ester by the solvent was well advanced before polarimetric readings were started. This was confirmed by further experiments.

A solution of 1·00 g. of racemic ester in ethyl (+)-tartrate (40 c.c.) was made at 80° and rapidly cooled to 25°, at which temperature it was kept for 30 minutes. Total precipitation by water gave an ester (0·98 g.) with $[\alpha]_{5461}^{25}$ −3·4° in AnalaR chloroform solution 2·5 minutes after being wetted with solvent (period of half-racemisation, 9 minutes).

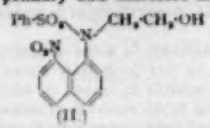
It would be expected that solvation and therefore optical activation would be less pronounced at 80° than at 25°. A solution of the ester (1·00 g.) in ethyl tartrate (40 c.c.) was made at 80° and kept at this temperature for 5 minutes and then at once treated with water. The recovered ester (0·95 g.) had $[\alpha]_{5461}^{25}$ −1·6° in chloroform solution 2·1 minutes after being wetted. Racemisation followed first-order kinetics.

In other experiments in which the ester was allowed to crystallise from a cooling solution in ethyl tartrate, various crops were obtained and were examined polarimetrically. The majority were optically inactive, but on one occasion a crop having a slight lævorotation was obtained. These crystallisation processes are, of course, not second-order asymmetric transformations, since the two possible solid phases are not diastereoisomeric in type: crystallisation could to some extent, however, be governed by chance inoculation.

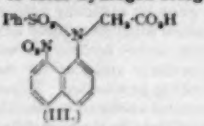
A solution of methyl *N*-benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylate in ethyl tartrate was kept for a day at room temperature and the total tribromo-ester recovered by addition of water. A chloroform solution of the ester had no optical activity. Conceivably the considerable steric factors in this ester prevent the union with the solvent which is possible with the less-hindered chloro-methyl-ester.

Hydrogen-bridging between alcohols offered a further field for investigation. In order to

obtain an alcohol which might be expected to possess suitable configurational stability and other desirable features, *8-nitro-N-benzenesulphonyl-N-(2-hydroxyethyl)-1-naphthylamine* (II) was synthesised by condensing 2-chloroethyl alcohol with 8-nitro-*N*-benzenesulphonyl-1-naphthylamide in presence of alcoholic alkali. The alcohol (II) has a number of advantageous properties: it is primary and therefore might be expected to form hydrogen-bridged structures



(II.)



(III.)

with hydroxylic solvents and it should have a configurational stability of an order similar to that of Mills and Elliott's acid (III) (*J.*, 1928, 1291). A solution of the alcohol (II) in ethyl (+)-tartrate was made at 80°, cooled, kept at 25° for 12 hours, and then treated with excess of water. The recovered alcohol had $[\alpha]^{20}_{5780}$ +9·1° in AnalaR chloroform solution 2·5 minutes after being wetted with solvent. Racemisation followed first-order kinetics (half-life, 27 minutes). Repetition of the experiment gave a product with $[\alpha]^{20}_{5780}$ +8·7° (half-life, 25 minutes). This is the only recorded example of a racemic substance, in which the optical activity has been *first* demonstrated by asymmetric solvent action.

A series of experiments was performed with alcohol (II) in other solvents, including *ethylene glycol* (−)-*menthyl ether*, an optically active primary alcohol specially synthesised for the purpose by reducing (−)-menthoxyacetic acid with ethereal lithium aluminium hydride. A solution of the alcohol (II) in the ether was kept for 2 days at room temperature and then treated with excess of light petroleum. The precipitated alcohol was, however, optically inactive.

Numerous experiments were conducted in order to detect possible optical activation of the alcohol (II) in solution in mixtures of chloroform with (+)- and (−)-*sec.*-octyl alcohols, (−)-menthyl glycollate, and (+)-citronellol. In each case the solution was kept in a temperature-controlled polarimeter tube. No mutarotational changes exceeding the probable experimental error were observed and total precipitation of the solute was not practicable.

Experimental.

Mutarotation of a Mixture of 2′-(2″-Hydroxy-2″-propyl)diphenyl-2-carboxylic Acid and (−)-sec.-Octyl Hydrogen Phthalate in Chloroform Solution.—(*a*) (−)-*sec.*-Octyl hydrogen phthalate (0·927 g.), dissolved in 7 c.c. of chloroform (B.P.), had α^{20}_{5780} −6·01° (*l* = 1; thermostatically controlled jacketted tube; temp. uncorr.). To this solution was added 0·853 g. of (±)-2′-(2″-hydroxy-2″-propyl)diphenyl-2-carboxylic acid, α^{20}_{5780} changing to −6·00°. This value changed during 5 days to −5·65°.

(*b*) The experiment was repeated at thermostat temperature [25·0° (corr.)], with use, as solvent, of B.P. chloroform washed with concentrated sulphuric acid to remove alcohol and subsequently washed with water and dried. (−)-*sec.*-Octyl hydrogen phthalate in this solvent had α^{20}_{5780} −6·18° (*l* = 1). The (±)-acid dissolved slowly during 21 hours, at the end of which α^{20}_{5780} was −6·05°, changing during the ensuing 3 days to −5·90°.

(*c*) 2·0 G. of (−)-*sec.*-octyl hydrogen phthalate were dissolved in 10 c.c. of chloroform (washed and dried as before) and mixed with a solution of 1·0 g. of the (±)-acid in 10 c.c. of chloroform. Approx. 12 c.c. of this solution were used in the polarimeter tube, the solution having α^{20}_{5780} −10·03° (*l* = 2). The rotation changed during 4 days to −9·47° and thereafter remained static. Addition of 0·80 g. of (+)-*sec.*-octyl hydrogen phthalate to this solution resulted in an immediate change in α^{20}_{5780} to −2·17°, which was constant for 3 days.

N-Benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic Acid with (−)-sec.-Octyl Hydrogen Phthalate in Chloroform.—1·00 G. of (−)-*sec.*-octyl hydrogen phthalate, dissolved in 7·5 c.c. of chloroform, had α^{20}_{5780} −5·88° (*l* = 1; thermostatically controlled tube; temp. uncorr.). To this solution was added 0·2 g. of (±)-*N*-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid; the rotation, measured within 2 minutes of mixing, was α^{20}_{5780} −6·11° and was unchanged after 24 hours. After this time a further 0·2 g. of (±)-acid was added; α^{20}_{5780} changed to −6·33°. A further 0·2 g. caused a change to 6·48°. No mutarotation was observed in any case.

Methyl N-Benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylate with (−)-sec.-Octyl Alcohol in Chloroform.—5 C.c. of (−)-*sec.*-octyl alcohol, mixed with 2 c.c. of chloroform, had α^{20}_{5780} −5·82° (*l* = 1; thermostatically controlled tube). 5 G. of (±)-methyl *N*-benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylate were added; α^{20}_{5780}, read within 5 minutes, was −5·69°. This value was unchanged in 24 hours.

Ethyl (+)-Tartrate.—It was found unsatisfactory to attempt to obtain the ester by vacuum-distillation of commercial samples. The ester was prepared by the method of Lowry and Cutter (*J.*, 1922, **121**, 832). It had α^{15}_{5780} +15·03° in a 2-dm. tube.

Ethylene Glycol (−)-Menthyl Ether.—A solution of (−)-menthoxyacetic acid (114 g.) in ether (300 c.c.) was gradually added to lithium aluminium hydride (20 g.) in ether (400 c.c.). Water and then dilute sulphuric acid were added and the ethereal layer was separated, dried, and distilled. The reduction product was distilled at 84—103°/3·5 mm. Redistillation gave 59 g., b. p. 100—101°/3·5 mm. (Found:

C, 71·8; H, 12·3. $C_{12}H_{24}O_3$ requires C, 71·9; H, 12·1%). The *ether* had d_4^{25} 0·9371 and α_{5461}^{25} −18·29° in a 2-dm. tube.

N-5-Nitrobenzenesulphonyl-N-(2-hydroxyethyl)-1-naphthylamine.—5-Nitro-*N*-benzenesulphonyl-1-naphthylamine (14 g.) was dissolved, by warming, in 70% aqueous ethyl alcohol (150 c.c.) containing potassium hydroxide (6 g.). 2-Chloroethyl alcohol (9 g.) was added and the mixture was heated in a pressure-bottle at 100° for 7 hours. The *product*, some of which had crystallised, was precipitated with water and filtered (13·6 g.). It crystallised from ethyl alcohol (charcoal) in pale yellow needles, m. p. 136—139° (74%) (Found: C, 58·5; H, 4·4; N, 7·3; S, 8·7. $C_{18}H_{16}O_5N_2S$ requires C, 58·1; H, 4·3; N, 7·5; S, 8·6%). The molecular weight was determined cryoscopically in ethylene dibromide:

Concn.	Mol. wt. found.	Association, %.
$8·7 \times 10^{-4}$ g.-mol./l.	386	7·2
$12·6 \times 10^{-4}$ „ „	419	22·4

The *acetate* was obtained from the above alcohol in almost quantitative yield by warming it with an excess of acetic anhydride in pyridine for 3 minutes. The mixture was cooled and poured into dilute hydrochloric acid; the gummy product eventually solidified and then crystallised from ethanol in cream-coloured, rhombic needles, m. p. 143—144° (Found: C, 58·3; H, 4·45; N, 6·7. $C_{20}H_{18}O_6N_2S$ requires C, 57·95; H, 4·4; N, 6·8%).

(−)-Menthyl glycollate, prepared by the esterification of glycollic acid with (−)-menthol, was purified by steam-distillation and crystallisation from aqueous alcohol. It had m. p. 88—89° and $[\alpha]_{5461}^{25}$ −97·3°, $[\alpha]_{5780}^{25}$ −86·0° (*c*, 25·06 in chloroform; *l* = 2).

(+)-Citronellol was kindly supplied by Messrs. A. Boake, Roberts and Co., Ltd. It was distilled before use and had b. p. 216°/745 mm., $[\alpha]_{5461}^{25}$ = +5·22°, $[\alpha]_{5780}^{25}$ = +4·57°.

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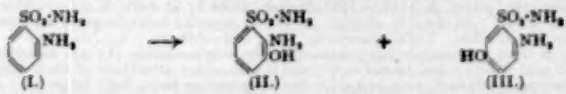
355. *The Synthesis of 2-Amino-3- and -5-hydroxybenzenesulphonamides.*

By D. V. PARKE and R. T. WILLIAMS.

2-Amino-3-hydroxybenzenesulphonamide has been synthesized from *m*-hydroxybenzenesulphonamide by way of 2-nitro-3-hydroxybenzenesulphonamide, and 2-amino-5-hydroxybenzenesulphonamide from *o*-aminobenzenesulphonamide by way of 5-bromo-2-aminobenzenesulphonamide. These compounds have been orientated and they appear to be identical with the two hydroxyorthanilamides which were isolated as metabolites of orthanilamide in the rabbit.

STUBBS AND WILLIAMS (*Biochem. J.*, 1947, **41**, xlix) reported the isolation of two aminohydroxybenzenesulphonamides from the urine of rabbits dosed with orthanilamide (I). These compounds were designated hydroxyorthanilamide-A (m. p. 188°) and -B (m. p. 179—180°) and were believed to be 2-amino-3- (II) and -5-hydroxybenzenesulphonamide (III) respectively, because the aromatic ring is usually hydroxylated *in vivo* in the positions *ortho* and *para* to the



(I.) (II.) (III.)

amino-group. An attempt was therefore made to synthesize these compounds through the corresponding nitro-derivatives which theoretically could be produced by the nitration of *m*-hydroxybenzenesulphonamide.

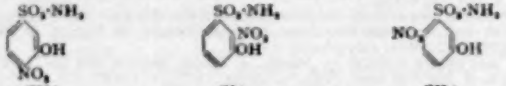
m-Hydroxybenzenesulphonamide was prepared by diazotization of *m*-aminobenzenesulphonamide and nitrated at 0° in concentrated sulphuric acid with 1·14 moles of nitric acid. A complex mixture of nitro-compounds was obtained in excellent yield. This was separated by chromatography, followed by fractional crystallization, into five pure compounds, two of which were mononitro- and three were dinitro-*m*-hydroxybenzenesulphonamides. These pure compounds accounted for some 20% of the starting material, 13% as mononitro- and 7% as dinitro-compounds. The main bulk of the mixture was, of course, sacrificed in the fractionation.

Theoretically *m*-hydroxybenzenesulphonamide could give rise on nitration to the 2-, 4-, and 6-mononitro-derivatives and probably to small amounts of the 2 : 4-, 2 : 6-, and 4 : 6-dinitro-derivatives. In this work we were only interested in the mononitro-compounds; the

dinitro-compounds were isolated incidentally and no attempt was made to determine their structure.

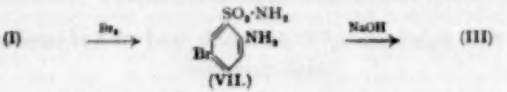
Although we expected to obtain three mononitro-derivatives we only succeeded in isolating two. Whether or not a third occurred in the mixed product could not be proved unequivocally. The least soluble mononitro-compound isolated formed dark yellow plates, m. p. 169—170°, and was readily proved to be 4-nitro-3-hydroxybenzenesulphonamide (IV) by reduction to the known 4-amino-3-hydroxybenzenesulphonamide which had been synthesized by Thorpe and Williams (*Biochem. J.*, 1941, **35**, 61) from benzoxazol-2-one.

The second mononitro-compound isolated formed pale yellow silky needles, m. p. 189—190°, and could be either 2-nitro-3- (V) or -5-hydroxybenzenesulphonamide (VI). On reduction, this nitro-compound yielded an amino-3-hydroxybenzenesulphonamide, m. p. 190°, which was identical (mixed m. p.) with the hydroxyorthanilamide-A isolated from rabbit urine. For reasons given below, this is the 2-amino-3-hydroxy-derivative (II) and therefore the mono-nitro-compound, m. p. 189—190°, is the 2-nitro-3-hydroxy-derivative (V).



(IV.) (V.) (VI.)

2-Amino-5-hydroxybenzenesulphonamide (III), m. p. 181°, was obtained from 5-bromo-2-aminobenzenesulphonamide (VII), prepared by bromination of orthanilamide in glacial acetic acid. The structure of (VII) was proved by heating it at 180° with 80% sulphuric acid whereby it was converted into *p*-bromoaniline. On fusion of (VII) with sodium hydroxide the hydroxy-



(VII.)

derivative (III), m. p. 181°, was obtained in poor yield. The structure of (III) follows from that of (VII). Hence by elimination the structure of the amino-derivative (II) and its parent nitro-derivative (V) is also proved. 2-Amino-5-hydroxybenzenesulphonamide appeared to be identical in all its reactions with the hydroxyorthanilamide-B of Stubbs and Williams (*loc. cit.*), but comparison by mixed melting point was not possible as none of the metabolite was available.

Experimental.

m-Hydroxybenzenesulphonamide.—Metanilamide (5 g.; m. p. 140°), dissolved in a mixture of sulphuric acid (20 c.c.) and water (40 c.c.), was diazotised at 0° with sodium nitrite (2 g.) in water (20 ml.) and then heated on the water-bath until the evolution of nitrogen ceased. After the mixture had been kept overnight at 0°, the crystals of *m-hydroxybenzenesulphonamide* were collected. A further quantity of the compound was obtained by exhaustively extracting the filtrate with ether (total yield, 4 g.). On recrystallization from water (charcoal), the sulphonamide was obtained as large, faintly yellow, thick, hexagonal plates, m. p. 165—166° (Found: C, 41·5; H, 4·05; N, 8·5; S, 19·0. $C_6H_7O_3NS$ requires C, 41·6; H, 4·1; N, 8·1; S, 18·5%). A strong aqueous solution gives a purple colour with dilute ferric chloride solution. Light absorption: $\lambda_{max.}$ 285—286 mμ.; $\varepsilon_{max.} = 2700$.

Nitration of m-Hydroxybenzenesulphonamide.—To the sulphonamide (10 g.), dissolved in concentrated sulphuric acid (65 c.c.) and cooled to 0°, was slowly added a mixture of nitric acid (4·2 c.c.; *d* 1·42) and concentrated sulphuric acid (4·5 c.c.), the temperature being kept below 5°. After an hour at room temperature, the mixture was poured on ice. The resulting yellow solution was extracted with ether which, when evaporated, left a yellow crystalline mass (11 g.). Repeated fractional crystallization of this product from water yielded only one pure compound—*4-nitro-3-hydroxybenzenesulphonamide*. This formed long dark yellow plates, m. p. 170° (Found: C, 33·3; H, 2·6; N, 12·9; S, 14·4. $C_6H_6O_5N_2S$ requires C, 33·0; H, 2·8; N, 12·9; S, 14·7%). It was slightly soluble in cold water but readily soluble in hot. It gives a deep orange colour with aqueous sodium hydroxide and a slight reddish-violet colour with aqueous ferric chloride.

The nitro-compound (0·4 g.) in water (10 c.c.) was heated with iron powder (1 g.) and dilute acetic acid (1 c.c.) until the yellow colour disappeared (*ca.* 10 minutes). The mixture was filtered and the filtrate continuously extracted with ether for 24 hours. The ether was evaporated off and the brown residue dissolved in a little ethanol and treated with charcoal. Carbon tetrachloride was then added to the filtered alcoholic solution until incipient precipitation occurred. The solution was warmed until the precipitate redissolved; on cooling, long pale brown plates, m. p. 164°, separated and were identified as 4-amino-3-hydroxybenzenesulphonamide by a mixed m. p. (164°) and colour reactions (cf. Thorpe and Williams, *loc. cit.*; Williams, *Biochem. J.*, 1946, **40**, 219; 1947, **41**, 1).

Chromatography of the Nitration Product.—The product of the nitration of *m*-hydroxybenzenesulphonamide was obviously complex. The crude nitration product obtained by ether-extraction as

above was dissolved in water and the solution poured on a column (1 × 40 cm.) of activated alumina (B.D.H.). The chromatogram was developed with water at pH 6. Two principal yellow bands developed, the upper consisting of dinitro- and the lower of mononitro-compounds.

The lower band was run off the column with water. The yellow solution was acidified with dilute hydrochloric acid, saturated with sodium chloride, and extracted with ether. Evaporation of the ether left a yellow crystalline solid which on fractional crystallisation from water yielded two compounds. The less soluble was 4-nitro-3-hydroxybenzenesulphonamide (m. p. 169—170°) described above. The more soluble 2-*nitro*-3-*hydroxybenzenesulphonamide* formed pale yellow, silky needles, m. p. 189—190° (Found: C, 33·0; H, 2·5; N, 12·9; S, 15·1. $C_6H_6O_5N_2S$ requires C, 33·0; H, 2·8; N, 12·9; S, 14·7%), readily soluble in water and giving a slight reddish-violet colour with aqueous ferric chloride and an orange colour with aqueous sodium hydroxide. The yields from 11 g. of nitration mixture were 4-nitro- 0·7 g. and 2-nitro- 0·58 g.

The 2-nitro-compound (0·3 g.) was reduced by heating it in water (8 c.c.) for a few minutes with iron powder (0·75 g.) and dilute acetic acid (0·7 ml.). Next morning, the solution was filtered and extracted continuously with ether. The ethereal extract was evaporated and the residue recrystallised from ethanol–carbon tetrachloride. Thus 2-*amino*-3-*hydroxybenzenesulphonamide*, m. p. 190°, was obtained (Found: C, 38·2; H, 4·25; N, 14·8; S, 16·6. $C_6H_8O_3N_2S$ requires C, 38·3; H, 4·3; N, 14·9; S, 17·0%) (see following paper for absorption spectrum). This compound gives a green colour with ferric chloride under certain conditions.

On diazotisation it gives an intense yellow colour, and coupling with dimethyl-α-naphthylamine takes place very slowly to give a red dye. It does not depress the m. p. (188°) of hydroxyorthanilamide-A (Found: C, 38·5; H, 4·7; N, 14·5; S, 16·7%) described by Stubbs and Williams (*loc. cit.*) from the urine of rabbits fed with orthanilamide and is identical with it in all respects.

The upper chromatogram band, on further development with water, was resolved into three bands, the lowest being pale lemon-coloured, the middle orange-yellow, and the uppermost mid-yellow. These bands were separated by cutting the column and extraction with water. Three *dinitro*-m-*hydroxybenzenesulphonamides* whose properties are given in the table were thus obtained.

Dinitro-m-*hydroxybenzenesulphonamides.*

No.	Location in upper band.	Description.	M. p.	Comparative solubility in water.	Yield, g.	Found, %: C.	H.	N.	S.
1	Middle	Dark yellow clusters	208—209°	Least soluble	0·08	27·8	1·95	15·9	12·25
2	Top	Short dark yellow needles	235	—	0·45	28·1	1·8	15·3	11·9
3	Bottom	Pale yellow short needles	248	Most soluble	0·18	25·7	2·55	15·1	—
				$C_6H_5O_7N_3S$ requires		27·4	1·9	16·0	12·2
				$C_6H_5O_7N_3S,H_2O$ requires		25·6	2·5	14·9	—

Reduction of the Nitration Product.—The separation of the components of the product of nitration of m-hydroxybenzenesulphonamide was extremely tedious and the final yields of the required amino-compounds small. Better yields, however, were obtained when the crude nitration product was first reduced and the amino-compounds separated.

A solution of the nitration product (20 g.) in hot water (250 c.c.) was boiled with iron powder (50 g.) and dilute acetic acid (5 ml.). A few crystals of sodium dithionite were added to the hot solution to reduce the black oxidation products of the aminophenolsulphonamides, and the solution was filtered hot and then continuously extracted with ether for 12 hours. Evaporation of the ether left a mixture of aminophenolsulphonamides, which was fractionated by crystallization from water after clarification with charcoal. During the crystallizations the solutions were kept in stoppered flasks and a few crystals of sodium dithionite were added. 2-Amino-3-hydroxybenzenesulphonamide (4 g.) separated first, as a mixture of red and yellow crystals (m. p. 190°) which were identical except in colour. From the mother-liquors, pale reddish-brown plates of 4-amino-3-hydroxybenzenesulphonamide (m. p. 164°; 0·1 g.) were obtained.

2-*Amino*-5-*hydroxybenzenesulphonamide.*—5-*Bromo*-2-*aminobenzenesulphonamide.* To orthanilamide (5·2 g.) in glacial acetic acid (75 c.c.), bromine (0·9 c.c., 2·8 g.) in acetic acid (15 c.c.) was gradually added during 5—10 minutes with gentle warming and vigorous shaking. After 15 minutes the solution was poured into water (250 c.c.), whereby the *bromo-orthanilamide* was precipitated; it was filtered off after several hours (4·2 g.). Repeated recrystallization from 25% aqueous ethanol gave the pure compound as almost white glistening elongated plates, m. p. 179° (Found: C, 28·5; H, 2·8; N, 10·5; Br, 33·0. $C_6H_7O_2N_2SBr$ requires C, 28·7; H, 2·8; N, 11·2; Br, 31·8%) (see Parke and Williams, *loc. cit.*, for absorption spectrum).

Conversion of 5-*bromo*-2-*aminobenzenesulphonamide into* p-*bromoaniline.* The foregoing bromo-compound (1 g.) in 80% sulphuric acid (10 ml.) was heated at 180° for 10 minutes. The pale pink solution gradually became violet, this colour gradually becoming more intense. After cooling, the solution was poured into water (50 c.c.) and neutralised with 40% aqueous sodium hydroxide, with cooling. When the solution was made slightly acid with dilute sulphuric acid, unchanged bromo-orthanilamide was precipitated; this was removed by filtration. The filtrate was made slightly alkaline with dilute sodium hydroxide solution, bromoaniline being precipitated. This was extracted with ether, and the extract dried (Na_2SO_4). Evaporation of the ether left *p*-bromoaniline as a violet solid which was dissolved in 2*N*-hydrochloric acid (5 c.c.) and water (20 ml.) by heat. After crystallization at 0°, *p*-bromoaniline hydrochloride separated as pale violet needles (220 mg., 28%). The free base was regenerated and after recrystallization from 20% aqueous ethanol formed nearly colourless clusters of needles (Found: Br, 47·0. Calc. for C_6H_6NBr: Br, 46·5%), m. p. 63—64° not depressed on admixture

with authentic *p*-bromoaniline (m. p. 64°). The free base (0·1 g.) was acetylated in the usual way and, after recrystallization of the product from 25% aqueous ethanol, *p*-bromoacetanilide (55 mg.), m. p. and mixed m. p. 166°, was obtained (Found: Br, 37·8. Calc. for C_8H_8ONBr: Br, 37·3%).

Conversion of 5-bromo-2-aminobenzenesulphonamide into 2-amino-5-hydroxybenzenesulphonamide. Sodium hydroxide (25 g.) and water (10 c.c.) were heated together in a silica dish and to the melt was added the 5-bromo-compound (5 g.) and sodium dithionite (1 g.). After being heated for a few minutes, the dark violet melt was allowed to cool and then dissolved in water. The solution was acidified with concentrated hydrochloric acid with cooling and then made neutral with saturated aqueous sodium carbonate. The solution (250 c.c.) was continuously extracted with peroxide-free ether for four periods of 8 hours each. Each ethereal extract was evaporated to dryness, and the residues were dissolved in a little hot water with the addition of little sodium dithionite, treated with charcoal, and filtered. The first extract gave only tars; the other three gave only tars on cooling, but, on concentration of the mother-liquors from these tars, 160 mg. (4·3%) of crude *2-amino-5-hydroxybenzenesulphonamide*, m. p. 179—180°, were obtained. Recrystallization from water eventually gave the pure compound, m. p. 180—181°, as violet-brown long plates (Found: C, 38·7; H, 4·3; S, 17·4. $C_6H_8O_3N_2S$ requires C, 38·3; H, 4·3; S, 17·0%). Light absorption: Maxima at 211, 255, and 338 mμ.; $\varepsilon_{max.}$ = 18,100, 7,800, and 3,200 respectively). It was readily soluble in hot water and moderately soluble in cold. With ferric chloride it gave an intense violet-red colour, soluble in ether. On addition of a drop of dilute aqueous ammonia to its aqueous solution, an intense violet colour gradually appeared; this colour is not given by 2- or 4-amino-3-hydroxybenzenesulphonamide, but is given by the metabolite, hydroxyorthanilamide-B. The same colour is also produced very slowly when an aqueous or ethanolic solution is exposed to air. Diazotization followed by coupling with dimethyl-α-naphthylamine gives an intense violet colour, as does that of *p*-aminophenol.

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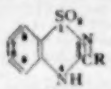
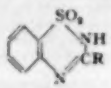
356. *Derivatives of Benz-1 : 2 : 4-thiadiazine 1 : 1-Dioxide.*

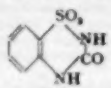
By D. V. Parke and R. T. Williams.

Orthanilamide and substituted orthanilamides when heated with urea at 180° give rise to 3-keto-3 : 4-dihydrobenz-1 : 2 : 4-thiadiazine 1 : 1-dioxide and its derivatives. It has been shown that in this reaction cyanic acid, formed by the decomposition of urea, combines with the orthanilamide to give a substituted urea which then cyclizes with loss of ammonia to form a benzthiadiazine. A number of benzthiadiazine 1 : 1-dioxide derivatives has been made by heating orthanilamides with formic acid at 100°. Observations on the spectra of these compounds have also been made.

Our interest in the chemistry of the benzthiadiazine system was aroused when one of us (Williams, *Biochem. J.*, 1945, **39**, xi), suspected that a crystalline compound (Found: C, 48·5; H, 5·3; N, 14·2; S, 16·0. Calc. for $C_8H_8O_3N_2S$: C, 48·95; H, 4·1; N, 14·3; S, 16·3%) which he had isolated in small amounts from the urine of rabbits dosed with orthanilamide (o-aminobenzenesulphonamide) was 3-methylbenz-1 : 4 : 2-thiadiazine 1 : 1-dioxide (I; R = Me) [this compound can also be formulated as a 1 : 2 : 4-thiadiazine (Ia)]. It was suspected that this


(I.)


(Ia.)

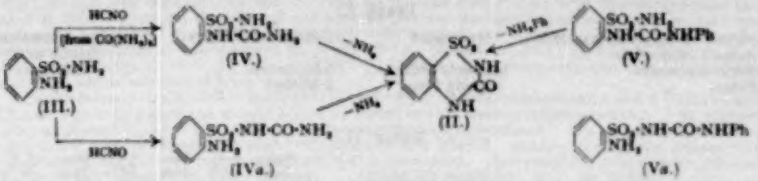

(II.)

compound had arisen by dehydration of acetylorthanilamide, a metabolite of orthanilamide. Only four compounds of this heterocyclic series had been recorded in the literature, namely, benz-1 : 2 : 4-thiadiazine 1 : 1-dioxide itself (I; R = H) and its 3-methyl and 3 : 4-dimethyl derivatives [Ekbom, *Bihang, K. Svenska Vet.-Akad. Handl.*, 1902, **27** (II), 3], and 3-keto-3 : 4-dihydrobenz-1 : 2 : 4-thiazine 1 : 1-dioxide (II) (Schräder, *J. pr. Chem.*, 1917, **95**, 392). It seemed of interest, therefore, to study further the chemistry of this type of compound.

The 3-keto-derivative (II) has a saccharin-like taste and was prepared by Schräder (*loc. cit.*) from saccharin by way of *o*-sulphonamidobenzoylazide during a Curtius rearrangement. We have found that it can very easily be prepared in excellent yield by heating orthanilamide with urea at about 180°. Substituted orthanilamides react similarly and we have prepared the 6-nitro-, 7-bromo-, and 5-hydroxy-derivatives of (II) from 4-nitro-, 5-bromo-, and 3-hydroxy-orthanilamide, respectively. 7-Nitro-3-keto-3 : 4-dihydrobenz-1 : 2 : 4-thiadiazine 1 : 1-dioxide was readily obtained by nitration of (II).

At the temperature of the reaction urea dissociates to ammonia and cyanic acid and therefore

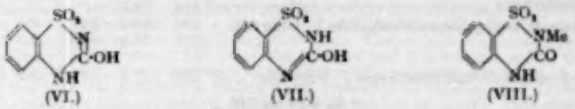
it appears likely that orthanilamide (III) actually combines with cyanic acid to give a substituted urea (IV or IVa), which could then lose ammonia to give (II). The possibility of the formation



of (IVa) in such a melt reaction has to be considered because, for example, White, Bratton, Litchfield, and Marshall (*J. Pharmacol.*, 1941, **72**, 112) have shown that, when sulphanilamide is fused with dicyanodiamide, the sulphonamide group is attacked and the product is mainly sulphanilylguanidine.

Support for this type of mechanism was obtained. *N*-Phenyl-*N'*-(*o*-sulphamylphenyl)urea (V) was prepared from orthanilamide and phenyl *iso*cyanate at 100°. When carefully heated, this decomposed to aniline and (II). When orthanilamide and phenyl *iso*cyanate are heated together, the formation of (Va) is possible; however, the product of the reaction appears to be (V), because it gave negative tests for an aromatic primary amino-group and was readily soluble in alkali but not in acid.

Two other possible structures (VI and VII) can be written for (II). We have been able to show, however, that the compound has the lactam structure (II). On methylation the lactim



structures (VI or VII) should yield a 3-methoxy-derivative (I or Ia; R = OMe) whereas the lactam structure should yield a *N*-methyl derivative, probably (VIII). With methyl sulphate and alkali, the compound yielded a monomethyl derivative which contained no methoxyl group (Zeisel method) and is probably 3-keto-2-methyl-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide (VIII). The ultra-violet absorption spectrum of this compound was very similar to that of (II) and quite different from that which would be expected for the lactim structure (VI or VII).

Compounds with the lactim structure (I or Ia; R = H) were readily obtained by heating orthanilamide or its substituted derivatives with formic acid at 100° (cf. Ekbom, *loc. cit.*). 5-Hydroxy-, 7-bromo-, and 6-nitro-benzthiadiazine 1 : 1-dioxide were prepared from 3-hydroxy-, 5-bromo-, and 4-nitro-orthanilamide respectively. The 3-methyl derivative (I or Ia; R = Me) was prepared by heating diacetylorthanilamide—it was originally prepared by Ekbom (*loc. cit.*) by heating monoacetylorthanilamide, but we were unable to prepare the monoacetyl derivative by heating orthanilamide on the water-bath with acetic anhydride according to his directions. We found that acetic anhydride and orthanilamide gave mainly diacetylorthanilamide. By use of equal volumes of acetic acid and acetic anhydride a mixture of acetyl derivatives was obtained, from which monoacetylorthanilamide could only be obtained with difficulty and in small yield. Monoacetylorthanilamide was readily transformed into 3-methylbenzthiadiazine 1 : 1-dioxide, even on recrystallization from hot water. Acetylation of orthanilamide with pyridine and acetic anhydride yielded diacetylorthanilamide almost quantitatively.

Since 3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide has a very sweet taste, the tastes of its derivatives are recorded in the Table I. Benzthiadiazine 1 : 1-dioxide derivatives not containing a keto-group were either tasteless or slightly bitter.

In the region 200—400 mμ. the ketodihydrothiadiazine 1 : 1-dioxides (II) in ethanol showed three absorption bands which appeared to correspond to those of the parent orthanilamide (III). The formation of the second ring with the introduction of a keto-group had little effect on the position of the maxima (see Table II), except for that of longest wave-length which is shifted in all cases to a shorter wave-length. The spectra of the benzthiadiazine 1 : 1-dioxides (I or Ia) in ethanol, however, were different from those of the keto-dihydro-derivatives (II). In general, the former showed two absorptions bands (Table III) instead of the three shown by the

keto-derivatives, in consequence, no doubt, of the introduction of a double bond into the heterocyclic ring.

TABLE I.

3-Keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	very sweet	7-Bromo-derivative	almost tasteless (faintly acid)
7-Nitro-derivative	intensely bitter	5-Hydroxy- ,,	tasteless
6-Nitro- ,,	slightly bitter	2-Methyl ,,	,,

TABLE II.

	$\lambda_{max.}$ mμ.	ε × 10^{-3}.	$\lambda_{max.}$ mμ.	ε × 10^{-3}.	$\lambda_{max.}$ mμ.	ε × 10^{-3}.
Orthanilamide	206	26·0	245—246	8·6	308	3·5
3-Keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	204 206	29·0 28·0	245	10·8	289	1·7
			(243	10·9	290	2·0) •
3-Keto-2-methyl-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	208 210	26·0 24·5	249	12·6	290	2·1
5-Bromo-orthanilamide	206	24·0	253	12·0	324	3·2
7-Bromo-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	206	24·6	256	14·5	305	1·7
4-Nitro-orthanilamide	—	—	238	18·9	382	2·2
6-Nitro-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	—	—	240 ~280	22·7 4·5	345	1·8
3-Hydroxyorthanilamide	210 224	24·6 23·0	~252	5·2	325	5·2
5-Hydroxy-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	210 (218	36·4 24·4	247 260	6·8 7·6	298 314	3·4 5·6) •
7-Nitro-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	205	17·2	~242	5·2	325 329	12·5 12·5

• In 0·1N-NaOH.

TABLE III.

Compound.•	$\lambda_{max.}$ mμ.	ε × 10^{-3}.	$\lambda_{max.}$ mμ.	ε × 10^{-3}.	$\lambda_{max.}$ mμ.	ε × 10^{-3}.
Benzthiadiazine 1 : 1-dioxide	207	13·4	269	7·6	—	—
3-Methyl derivative	214	8·8	266	7·9	—	—
7-Bromo- ,,	215	10·9	291	13·1	—	—
6-Nitro- ,,	216	6·2	261 266	15·6 16·1	~292 368	10·4 1·35

• In ethanol.

EXPERIMENTAL.

Absorption spectra were determined with a Unicam Quartz Spectrophotometer, Model S.P. 500. M. p.s are uncorrected.

3-Keto-3 : 4-dihydrobenz-1 : 2 : 4-thiadiazine 1 : 1-Dioxide Derivatives.—*3-Keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide.* Orthanilamide (10 g.) and urea (7 g.) were intimately mixed and heated to 180°. Ammonia was evolved and after 30 minutes the mixture suddenly crystallised. The product was cooled and dissolved in hot water (100 c.c.), treated with charcoal, and filtered. On acidification of the solution with dilute hydrochloric acid, the compound crystallized. After an hour at 0°, the white crystals were filtered off, washed with water, and dried (10·4 g., 94%). The compound (colourless needles) was purified by recrystallization from water containing a little ethanol. It had a very sweet saccharin-like taste and m. p. 305° (Schräder, *loc. cit.*, gives m. p. 287—288°) (Found: C, 42·8; H, 3·1; N, 14·1. Calc. for $C_7H_6O_3N_2S$: C, 42·4; H, 3·0; N, 14·1%). The substance was acidic and dissolved in sodium carbonate solution with effervescence.

On methylation with methyl sulphate and alkali, it gave *3-keto-2-methyl-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide* in poor yield as white needles, m. p. 238—240°, from aqueous ethanol (Found: C, 45·0; H, 3·8; N, 12·9; OMe, 0. $C_8H_8O_3N_2S$ requires C, 45·3; H, 3·8; N, 13·2; OMe, 0%).

7-Nitro-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide. The 3-keto-derivative (10 g.) was dissolved in concentrated sulphuric acid (10 c.c.) and nitrated at 0—5° with a mixture of concentrated nitric (3·5 c.c.) and sulphuric acids (4 c.c.). The product was poured on ice and the solid which separated was filtered off and washed with ice-water. On recrystallization from hot water, the *nitro*-compound was obtained as pale buff-coloured plates, m. p. 283° (9 g.) (Found: N, 17·1; S, 12·9. $C_7H_5O_5N_3S$ requires N, 17·3; S, 13·2%). With 10% aqueous sodium hydroxide it formed a deep-orange *sodium* salt, insoluble in strong alkaline solution (Found: Na, 8·8. $C_7H_4O_5N_3SNa$ requires Na, 8·7%). When heated, the salt

became red, and when it was kept for a few hours in the cold the orange colour returned. When kept for a few months the salt became nearly white.

6-*Nitro*-3-*keto*-3 : 4-*dihydrobenzthiadiazine* 1 : 1-*dioxide*. 4-Nitro-2-aminobenzenesulphonamide (0·8 g.) (Thorpe and Williams, *Biochem. J.*, 1941, **35**, 61) and urea (0·7 g.) were intimately mixed and heated at 200°. Ammonia was evolved and after 15 minutes the melt crystallised. The product was dissolved in hot water; the solution was treated with charcoal and filtered. On cooling the **6-*nitro***-compound crystallised as yellow prisms, m. p. 270° (0·7 g.) (Found: C, 34·7; H, 2·0; N, 16·9; S, 12·5. $C_7H_5O_5N_3S$ requires C, 34·6; H, 2·1; N, 17·3; S, 13·2%). This compound also formed an orange sodium salt which became red when heated.

7-*Bromo*-3-*keto*-3 : 4-*dihydrobenzthiadiazine* 1 : 1-*dioxide*. Bromo-orthanilamide (0·5 g.) (Parke and Williams, preceding paper) and urea (0·5 g.) were heated to 150°, ammonia being evolved. The temperature was allowed to rise to 200° and after 10 minutes the melt crystallised. The product was dissolved in hot water and the solution treated with charcoal and filtered. Acidification of the filtrate with hydrochloric acid gave the 7-***bromo***-compound (0·45 g.) as needles. Recrystallised from aqueous ethanol, it had m. p. 335° (Found: N, 10·1; Br, 29·4. $C_7H_5O_3N_3SBr$ requires N, 10·1; Br, 28·8%).

5-*Hydroxy*-3-*keto*-3 : 4-*dihydrobenzthiadiazine* 1 : 1-*dioxide*. 2-Amino-3-hydroxybenzenesulphonamide (229 mg.) intimately mixed with urea (150 mg.) was heated at 180° for 1 hour. The product was boiled with water (charcoal) and filtered. On acidification, the filtrate yielded the **5-*hydroxy***-compound (160 mg., 61%) as white needles, m. p. 275°. It gave a deep-blue colour with ferric chloride, was sparingly soluble in cold water, and titrated as a monobasic acid (Found: C, 39·7; H, 2·9; N, 12·7; S, 15·0; equiv., 219. $C_7H_6O_4N_3S$ requires C, 39·25; H, 2·8; N, 13·1; S, 15·0%; equiv., 214). Acetylation with acetic anhydride gave the **5-*acetyl*** derivative as short colourless needles, m. p. 262°, after recrystallization from water (Found: $CH_3{\cdot}CO$, 17·0. $C_9H_8O_5N_3S$ requires $CH_3{\cdot}CO$, 16·8%).

N-*Phenyl*-N'-(o-*sulphamylphenyl*)*urea*.—Equal weights of orthanilamide (2 g.) and phenyl isocyanate were heated together at 100°. The mixture became pasty and then solidified. After an hour, the solid was dissolved in hot ethanol (charcoal) and filtered, and crystallization induced by dilution with water (yield, 2 g.). The substituted ***urea*** was recrystallised from aqueous ethanol and formed soft matted needles, m. p. 180° (Found: C, 54·1; H, 4·7; N, 14·1. $C_{13}H_{13}O_3N_3S$ requires C, 53·6; H, 4·5; N, 14·4%). This substance gave no colour when diazotized and coupled with alcoholic dimethyl-α-naphthylamine. It readily dissolved in dilute aqueous sodium hydroxide, but was sparingly soluble in dilute hydrochloric acid.

***Action of Heat on* N-*Phenyl*-N'-(o-*sulphamylphenyl*)*urea*.**—The foregoing compound (0·5 g.) was heated at 220° for an hour in a test-tube with a side-arm. Aniline distilled off (identity proved by colour reactions) and was collected in 5 c.c. of 10% sulphuric acid. The solution of aniline sulphate was made alkaline and extracted with ether. The ether was removed and the residual aniline converted into acetanilide (22 mg.), m. p. 112° not depressed by admixture with authentic acetanilide, m. p. 115°. The residue in the test-tube was dissolved in boiling water, treated with charcoal, and filtered. On acidification with hydrochloric acid and cooling, 280 mg. of pink needles, m. p. 295°, were obtained. These, on recrystallization from water (charcoal), formed colourless needles which were identified by absorption spectra and mixed melting point as 3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide.

***Benz*-1 : 4 : 2-*thiadiazine* 1 : 1-*Dioxide Derivatives*.**—These compounds were prepared by heating the appropriate orthanilamide derivative with an equal weight of anhydrous formic acid for an hour on the water-bath. The product was poured into water and the crystals filtered off.

The following were prepared: **6-*Nitrobenzthiadiazine* 1 : 1-*dioxide***, obtained in quantitative yield from 4-nitro-2-aminobenzenesulphonamide (0·12 g.) and formic acid (0·2 c.c.), formed six-sided yellow plates, m. p. 358° (decomp.), which were very sparingly soluble in water (Found: C, 35·7; H, 2·5; N, 17·8. $C_7H_5O_4N_3S{,}0{\cdot}5H_2O$ requires C, 35·6; H, 2·6; N, 17·8%). Its colour was not intensified on addition of 2N-sodium hydroxide. The **7-*bromo***-compound (from 5-bromo-orthanilamide) formed plates, m. p. 285°, from ethanol (Found: C, 32·8; H, 1·9; N, 10·1; Br, 28·5. $C_7H_4O_3N_3SBr$ requires C, 32·2; H, 1·9; N, 10·7; Br, 30·6%). The **5-*hydroxy***-compound (from 3-hydroxyorthanilamide) formed light-brown prisms, m. p. 263°, from water (Found: C, 42·6; H, 3·2; N, 14·05; S, 16·3. $C_7H_5O_3N_3S$ requires C, 42·4; H, 3·05; N, 14·1; S, 16·2%). It gave a blue colour with ferric chloride. Benzthiadiazine 1 : 1-dioxide, m. p. 222°, was prepared according to Ekbom's directions (*loc. cit.*; he gives m. p. 219—220°) from orthanilamide and formic acid.

3-*Methylbenzthiadiazine* 1 : 1-*Dioxide*. *Acetylation of Orthanilamide*.—Orthanilamide (5 g.) was added to a mixture of pyridine (5 c.c.) and acetic anhydride (10 c.c.). The amide dissolved in 5 minutes and the mixture became warm. Next morning, the o-diacetylaminobenzenesulphonamide was filtered off, washed with water (yield, 4·8 g.), and recrystallised from hot water; it formed prisms, m. p. 190° (Found: C, 47·3; 4·9; N, 10·6. Calc. for $C_{10}H_{12}O_4N_2S$: C, 46·9; H, 4·7; N, 10·9%); Ekbom (*loc. cit.*) gives m. p. 191·5—192·5°. When heated for 2 hours at 200° it yielded 3-methylbenzthiadiazine 1 : 1-dioxide, m. p. 269° (Ekbom gives m. p. 263—264°).

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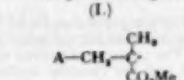
357. *Properties and Reactions of Free Alkyl Radicals in Solution. Part I. Some Reactions of 2-Cyano- and 2-Carbomethoxy-2-propyl Radicals with Quinones.*

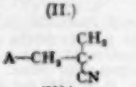
By A. F. Bickel and W. A. Waters.

The free radicals $Me_2\dot{C}\cdot CO_2Me$ and $Me_2\dot{C}\cdot CN$ can be formed by the thermal decomposition of dimethyl αα′-azo*iso*butyrate (I) and αα′-azo*iso*butyronitrile (II) in boiling toluene. Their reactions with quinones have been studied with the object of gaining direct information concerning the natures of the chain-stopping and rate-retarding actions of quinones in olefin polymerization. It is found that *p*-benzoquinone and chloranil react with these tertiary alkyl radicals to give both mono- and di-ethers of quinol and tetrachloroquinol respectively, whilst 2-methyl-1 : 4-naphthaquinone and some αβ-unsaturated aldehydes and ketones do not appear to react. The significance of this work is discussed in connection with the free-radical polymerization of olefins.

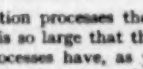
The thermal decomposition, in solution, of aliphatic azo-compounds such as dimethyl αα′-azo-*iso*butyrate (I) and αα′-azo*iso*butyronitrile (II) yields free tertiary alkyl radicals. These radicals are capable of initiating polymerization and are very similar in structure to the growing radicals which are concerned in the polymerization of vinyl compounds (Bickel and Waters, *Rec. Trav. chim.*, 1950, **69**, 312, in the press). The radical (III; A = H) for instance can be regarded as the end group of a growing poly(methyl methylacrylate) radical, and similarly the radical (IV; A = H) is the prototype of the growing chain of poly(methylacrylonitrile).



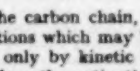
(I.)



(II.)



(III.)



(IV.)

When polymerization processes themselves are studied the carbon chain, represented by A in (III) and (IV), is so large that the many chemical reactions which may be concerned in chain-terminating processes have, as yet, been investigated only by kinetic methods. This physico-chemical approach is incapable of revealing more than the activation energies and probabilities of occurrence of reactions of different types, *e.g.*, radical combination, disproportionation of two radicals, chain transfer; it can give very little precise information about the structural arrangement at the chain-terminating end of a macromolecule. Information of this character is particularly important in the study of polymerizations which have been controlled deliberately by the addition of " radical inhibitors " or " retarding agents " such as quinones or aromatic nitro-compounds or have been modified by the admixture of chain-transfer agents or co-polymerizing substances. The spectroscopic study of these modified macromolecules gives, at the best, an uncertain impression of the structures of their end groups since the modifying group composes such a small part of the whole molecule that distinctive absorption bands appear only with low intensity. Moreover, it may be impossible to discriminate between isomeric structures, or between mono- and di-substituted products. Again, unless a tedious separation of fractions of different molecular-weight range has previously been carried out, it may well be that some part of the modifying agent remains chemically intact though mechanically entangled in the polymer.

However, if it can be presumed that the simple radicals (III) and (IV), where A = H, will behave in a very similar way to the analogous macromolecular radicals, then the structures of the end groups of macromolecules can be deduced by the exact methods of experimental organic chemistry. We have already shown (Bickel and Waters, *loc. cit.*) that the decomposition of aliphatic azo-compounds in the inert solvents benzene and toluene indicates that the termination of radicals of type (III) proceeds by combination and disproportionation processes in comparable amounts, but that the latter process is much less probable with radicals of type (IV).

Knowing the products which can be formed by the thermal decompositions of (I) and (II) themselves, we have now proceeded to examine the substances which they yield when decomposed in boiling toluene, in the presence of *p*-benzoquinone and similar compounds, and we have been successful in isolating and characterizing crystalline reaction products which clearly indicate

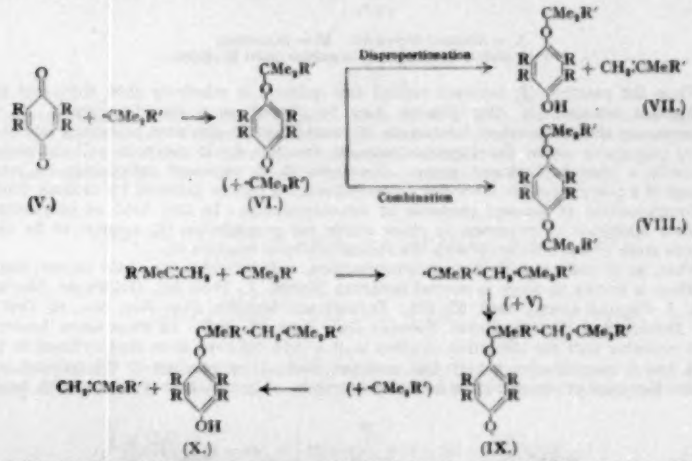
the course of free radical–inhibitor molecule interactions. The success of our method is such that we propose to develop it further for the elucidation of other problems concerning free-radical polymerization processes.

When dimethyl αα′-azo*iso*butyrate (I) is decomposed in boiling toluene with an equimolar proportion of *p*-benzoquinone (V; R = H), quinol mono-(2-carboxymethyl-2-propyl) ether (VII; R = H, R′ = CO_2Me) and quinol di-(2-carboxymethyl-2-propyl) ether (VIII; R = H, R′ = CO_2Me) are formed in yields of 46 and 27% respectively. The di-ether could be isolated as such from the reaction mixture, but extraction of the mono-ether with alkali results in its hydrolysis to the corresponding acid. This compound on methylation with diazomethane yields the methyl ether of (VII; R = H, R′ = CO_2Me), whilst on oxidation with ferric chloride *p*-benzoquinone is formed. These reactions clearly prove the structure of (VII; R = H, R′ = CO_2H) and exclude the possibility of substitution by the radical in the benzene ring.

When αα′-azo*iso*butyronitrile (II) is used, the quinol mono-ether (VII; R = H, R′ = CN) is again obtained in a yield of 40%, but the di-ether is formed in a yield of 10% only. Furthermore the benzoate of a compound, probably (X), could be isolated in a 3% yield.

When (II) is allowed to decompose in boiling toluene containing half an equivalent of chloranil (V; R = Cl), there is no abstraction of chlorine atoms from the latter. Again both the mono- (VII; R = Cl, R′ = CN) and the di-ether (VIII; R = Cl, R′ = CN) of tetrachloroquinol are formed, showing that the radical attack is upon the oxygen atoms only, but in this case the yield of the di-ether (47%) is much larger than that of the mono- (17%).

The formation of all these compounds is satisfactorily explained by assuming the primary production of semiquinone radicals of type (VI) or (IX). These will either combine or disproportionate with the tertiary alkyl radicals of type (III) and (IV). The methyl methylacrylate or methylacrylonitrile formed in the disproportionation reaction is not found as such, but is probably incorporated in neutral material of high molecular weight which is formed to the extent of 20—40% in these reactions.

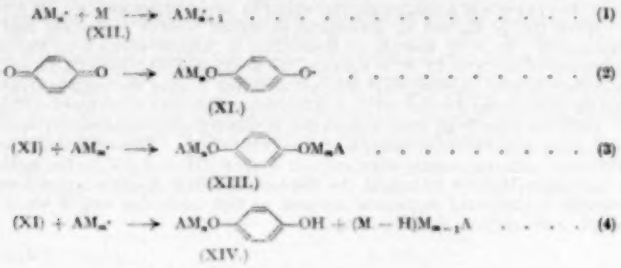


2-Methyl-1 : 4-naphthaquinone was not attacked by the radicals derived from (II), and neither were mesityl oxide and cinnamic aldehyde, both of which contain the reactive catio-enoid system C=C—C=O to which much of the characteristic chemical reactivity of quinones has been ascribed. Finally it was established that the radicals (III; A = H) do not react with quinol.

It is significant therefore that the free radicals (III) and (IV) (A = H) have a sufficient degree of reactivity to attack only highly active quinones. An explanation for the relative inhibiting actions of different quinones can therefore be sought by extending the present work to the examination of the products obtainable from a series of substituted quinones.

Our work does not confirm several of the speculations concerning the modes of action of quinones as inhibitors, retarders, or chain-transfer agents in the chain polymerization of olefins.

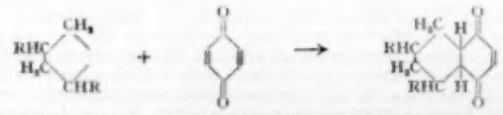
The nuclear substitution of quinones, to give quinonoid products, has been proposed by Price ("Reactions at Carbon-Carbon Double Bonds," Interscience, New York, 1946, pp. 85—87), and others, who have based their judgments on the behaviour of such intensely reactive free radicals as methyl and phenyl. Thus benzenediazonium chloride reacts with *p*-benzoquinone to give 2-phenylbenzoquinone (Kvalnes, *J. Amer. Chem. Soc.*, 1934, **56**, 2478), whereas diacyl peroxides of both the aliphatic and the aromatic series react with 2-methyl-1 : 4-naphthaquinone to give 3-substituted products (Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2060). In contrast to this it has long been known that the resonance-stabilised radical triphenylmethyl combines with *p*-benzoquinone to give the bistriphenylmethyl ether of quinol. Our tertiary radicals (III) and (IV) (A = H), which closely resemble the corresponding macroradicals, behave similarly in yielding quinol mono- and di-ethers. It would appear therefore, that Price's explanation of the manner of retardation by quinones cannot be correct in the case of tertiary macro-radicals. Instead the mechanism must involve semiquinone radicals of type (XI), which may combine or disproportionate with radicals (XII) to yield (XIII) and (XIV).



A = initiator fragment. M = monomer.
n and *m* = number of monomer units in chain.

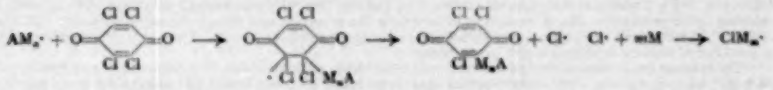
When the reaction (2) between radical and quinone is relatively slow compared to the propagation reaction (1), the quinone may be classed as a retarding agent. In these circumstances the combination mechanism (3) would lead to polymers possessing one di-ether system per chain, whilst the disproportionation reaction would result in half the molecules containing a phenolic hydroxyl group. Reactions (2—4) represent retardation by *p*-benzoquinone of a polymerization involving mono-radicals, *e.g.*, those initiated by radicals produced by decomposition of benzoyl peroxide or azo-compounds. In this kind of polymerization complete inhibition is unknown, in other words the propagation (1) appears to be able to compete more or less effectively with the radical-inhibitor reaction (2).

When, as in thermal and photo-polymerizations, a di-radical is the chain carrier, complete inhibition is known to occur in several instances (Foord, *J.*, 1940, **48**; Goldfinger, Skeist, and Mark, *J. Physical Chem.*, 1943, **47**, 578; Burnett and Melville, *Proc. Roy. Soc., A*, 1947, **189**, 456; Melville and Watson, *Trans. Faraday Soc.*, 1948, **44**, 886). In these cases, however, it seems probable that the inhibition reaction is of a type different from that outlined in (1—4) above and it may involve a very fast modified Diels–Alder reaction of the quinone with a dimeric di-radical produced by the initiation reaction. The structure of this product, however,

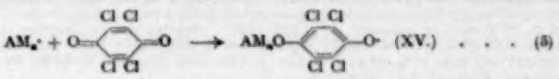


has never been established with certainty (Kern and Feuerstein, *J. prakt. Chem.*, 1941, **158**, 186; Melville and Watson, *loc. cit.*). It is surprising that the photo-polymerization of methyl methylacrylate in the presence of *p*-benzoquinone, which has been investigated by Mackay and Melville (*Trans. Faraday Soc.*, 1950, **46**, 63), shows retardation instead of inhibition. This they attributed to an unsuitable configuration of the dimeric di-radical caused by the presence of the methyl groups. Our reactions (2—4) will probably be valid for this retardation process.

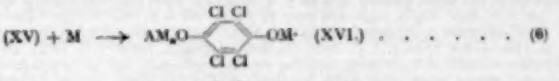
The formation from chloranil of both the mono- and the di-substituted ethers of tetrachloroquinol has an important bearing on polymer chemistry. It is known that the addition of chloranil to a polymerizing system may result in a polymer of considerably lower molecular weight than is normal, though the rate of polymerization is not greatly affected. In other words chloranil acts as a chain-transfer agent and not as an inhibitor. It has been suggested (Price, *loc. cit.*) that in these cases chloranil behaves like carbon tetrachloride by providing chlorine atoms to start new radical chains:

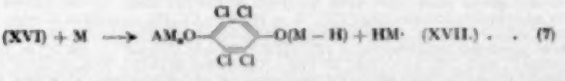


Evidently this mechanism is incorrect, since the radicals (IV; A = H) react with chloranil at the oxygen atoms only, and the reaction process (*b*) must therefore proceed *via* a semiquinol radical (XV). To explain the chain transfer we suggest that (XV) can add on monomer to give a

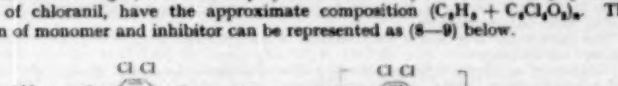


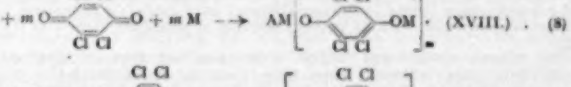
radical (XVI), which in turn may react with monomer to yield (XVII) and a new initiating radical. This scheme is still mainly hypothetical, but it is supported by the fact that radicals of type (XVI) seem to react rather with unsaturated molecules than with radicals $AM_n^{\cdot}$. This



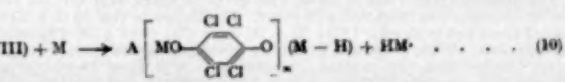


follows from work by Breitenbach *et al.* (*Ber.*, 1943, **76**, 272, 1088), who have shown that the polymers of low molecular weight, obtained on polymerization of styrene with benzoyl peroxide in the presence of chloranil, have the approximate composition $(C_8H_8 + C_6Cl_4O_2)_n$. This co-polymerization of monomer and inhibitor can be represented as (8—9) below.





The co-polymer chains should then be terminated mainly (*a*) by radicals of type (XVIII) reacting with monomer to yield (according to 10) products of type (XX) together with an



initiating radical, and (*b*) to a small extent by radicals of type (XIX) reacting with radicals $AM_n^{\cdot}$ to yield either, by disproportionation, a polymer with a phenolic hydroxyl end group or else a combination product.

There are indications that *p*-benzoquinone may also be co-polymerized by some monomers. A reaction of this kind would account for the greatly increased rate of photo-polymerization of butyl acrylate in the presence of *p*-benzoquinone (Melville and Bickel, *Trans. Faraday Soc.*, 1949, **45**, 1049).

Our observation that quinol, like phenol (Bickel and Waters, *loc. cit.*), did not react with the 2-carbomethoxy-2-propyl radical is in accord with the findings of Breitenbach, Springer, and Horeischy (*Ber.*, 1938, **71**, 1438) who stated that quinol does not inhibit the polymerization of styrene in the complete absence of oxygen.

Experimental.

Reaction of Dimethyl aa'-Azoisobutyrate with p-Benzoquinone.—A solution of dimethyl aa'-azoisobutyrate (9·2 g.) and *p*-benzoquinone (2·16 g.) in toluene (50 ml.) was heated to about 100° in such a manner as to produce a steady evolution of nitrogen (30 minutes) and then refluxed for 1 hour. To the cold red solution was added an aqueous solution of sodium sulphite (2 g.). Then it was extracted with a solution of sodium hydroxide (2·5 g.) in water.

The toluene layer was subjected to fractional distillation and fractions, b. p. 100—115° and 200—220° (2·5 g.), were collected. The first fraction was hydrolysed and was found to contain 0·5 g. of methyl isobutyrate. The second consisted of almost pure dimethyl tetramethylsuccinate. The residue on distillation in a high vacuum gave an orange oil (3·2 g.), b. p. 120—140°/0·1 mm. This product was mixed with potassium hydroxide (2 g.), ethanol (10 ml.), and water (10 ml.), and the resulting solution was refluxed for 16 hours. The ethanol was distilled off, the residue acidified, and the dark brown oil that separated was dissolved in ether. Evaporation of the ether yielded a slowly crystallizing oil. Recrystallization from ethyl acetate gave *quinol di-(2-carboxy-2-propyl) ether* (VIII; R = H, R′ = CO_2H) (1·5 g., 27% calc. on quinone), m. p. 182—186°. Further recrystallization raised the m. p. to 186—188° (Found: C, 59·3; H, 6·4. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). The derived *di-p-nitrobenzyl* ester, recrystallized from 70% ethanol, had m. p. 103—104° (Found: C, 60·9; H, 4·8; N, 5·3. $C_{28}H_{28}O_{12}N_2$ requires C, 60·9; H, 5·1; N, 5·1%).

The aqueous layer was acidified and extracted with ether. Evaporation of the ether gave a brown crystalline residue (1·8 g., 46% calc. on quinone). After recrystallization from ethyl acetate the m. p. of *quinol mono-(2-carboxy-2-propyl) ether* (VII; R = H, R′ = CO_2H) was 161·5—162·5° (Found: C, 61·3; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%). The *amide* of (VII, R = H, R′ = CO_2H), prepared in the usual manner, had m. p. 173—173·5° after recrystallization from water (Found: C, 61·8; H, 7·0; N, 6·8. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2%). The compound (VII; R = H, R′ = CO_2H) gave a *dibenzoyl* derivative which was recrystallized 3 times from ethanol and then had m. p. 113—114·5° (Found: C, 70·9; H, 5·2. $C_{24}H_{20}O_6$ requires C, 71·3; H, 5·0%). This product was insoluble in sodium hydroxide solution so that evidently the carboxyl group as well as the phenolic hydroxyl group must have been involved in the reaction. *Quinol methyl (2-carbomethoxy-2-propyl) ether* was obtained by treating (VII; R = H, R′ = CO_2H), suspended in ether, with an excess of ethereal diazomethane solution. The ether was evaporated and the residue distilled in a high vacuum. The almost colourless liquid boiled at 120—124°/0·75 mm. (Found: C, 64·6; H, 7·6; OMe, 28·4. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2; OMe, 27·7%). Oxidation of (VII; R = H, R′ = CO_2H) with a large excess of ferric chloride at 100° yielded *p*-benzoquinone, which was isolated in 50% yield by steam-distillation and extraction, with ether, of the distillate. The mixed m. p. with pure *p*-benzoquinone showed no depression. The same yield of mono-ether may be obtained by extraction of the reaction mixture with alkali only. It is advisable, however, to reduce a small amount of unreacted *p*-benzoquinone first by adding some sodium sulphite.

The same yields of products were obtained when equimolar quantities of azo-compound and *p*-benzoquinone were used.

Reaction of aa'-Azoisobutyronitrile with p-Benzoquinone.—A solution of aa'-azoisobutyronitrile (16·4 g.) and *p*-benzoquinone (10·8 g.) in toluene (100 ml.) was refluxed for 30 minutes. When cold, the dark red solution was extracted with an aqueous solution of potassium hydroxide (11 g.) and sodium sulphite (2 g.).

The toluene solution was distilled with steam and from the distillate 3·5 g. of tetramethylsuccinonitrile were isolated. The residue from the steam-distillation was a brown tarry mass. Recrystallization from ethanol gave *quinol di-(2-cyano-2-propyl) ether* (VIII; R = H, R′ = CN) (2·5 g., 10% calc. on quinone), m. p. 123—126°. Recrystallization from acetone raised the m. p. to 128—129° (Found: C, 68·8; H, 6·6; N, 11·8. $C_{14}H_{16}O_2N_2$ requires C, 68·8; H, 6·6; N, 11·5%). The corresponding acid was obtained by alkaline hydrolysis of the dinitrile and after recrystallization from ethyl acetate had m. p. 186—188°. A mixed m. p. with the di-acid, obtained from the experiment with dimethyl aa'-azoisobutyrate showed no depression.

The aqueous extract was acidified with dilute sulphuric acid and the resulting oil (10·0 g., 56·5% calc. on quinone) was extracted with ether. Distillation of this oil in a high vacuum produced *quinol mono-(2-cyano-2-propyl) ether* (VII; R = H, R′ = CN) (7·15 g., 40·5% calc. on quinone), b. p. 129—135°/0·08 mm. When subjected to alkaline hydrolysis this oil gave an acid, m. p. 161·5—162·5° after recrystallization from ethyl acetate. A mixed m. p. with the mono-ether prepared from the experiment with dimethyl aa'-azoisobutyrate showed no depression. Benzoylation of the nitrile (VII; R = H, R′ = CN) gave a *monobenzoate*, m. p. 86·5—87·5° after recrystallization from ethanol (Found: C, 72·6; H, 5·5; N, 4·8. $C_{11}H_{10}O_2N$ requires C, 72·6; H, 5·4; N, 5·0%). In another experiment the crude product (10·0 g.) obtained by acidifying the aqueous layer was benzoylated with 20 ml. of benzoyl chloride and 150 ml. of 10% sodium hydroxide. The crude benzoates on recrystallization from ethanol gave the benzoate, m. p. 86·5—87·5° (8·0 g.) (see above). The mother-liquor on concentration yielded the *benzoate*, m. p. 117—121° (1·0 g., 3% calc. on quinone) of (X; R = H, R′ = CN). Further recrystallization from ethanol raised the m. p. to 123—124° (Found: C, 72·3; H, 5·5; N, 7·9. $C_{21}H_{16}O_4N_2$ requires C, 72·4; H, 5·8; N, 8·0%).

Reaction of aa'-Azoisobutyronitrile with Chloranil.—A solution of aa'-azoisobutyronitrile (8·2 g.) and chloranil (6·15 g.; recrystallized from chlorobenzene) in chlorobenzene (150 ml.) was heated at 100° until

evolution of nitrogen stopped (30 minutes) and then refluxed for 5 minutes. The cold light-brown solution was extracted with an aqueous solution of sodium hydroxide (2·5 g.) and sodium sulphite (0·5 g.).

The chlorobenzene layer was distilled with steam and yielded tetramethylsuccinonitrile (3·0 g.). The residue was collected by filtration and dried (6·4 g.). Recrystallisation from a large volume of ethanol gave *tetrachloroquinol di-(2-cyano-2-propyl) ether* (VIII; R = Cl, R′ = CN), m. p. 162—166° (4·5 g., 47% calc. on quinone), raised to 166—167° by recrystallisation from acetone (Found: C, 44·2; H, 3·3; N, 7·2; Cl, 36·2. $C_{16}H_{16}O_2N_2Cl_4$ requires C, 44·0; H, 3·2; N, 7·3; Cl, 37·1%).

After addition of an excess of dilute sulphuric acid the aqueous layer yielded a crystalline precipitate. *Tetrachloroquinol mono-(2-cyano-2-propyl) ether* (VII; R = Cl, R′ = CN) was filtered off and dried (1·35 g., 17% calc. on quinone). After recrystallisation from ethanol, the m. p. was 135° (decomp.) (Found: C, 38·3; H, 2·2; N, 4·4; Cl, 45·6. $C_{10}H_7O_2NCl_4$ requires C, 38·1; H, 2·2; N, 4·5; Cl, 45·0%). The *benzoate* (of VII; R = Cl, R′ = CN), recrystallized from ethanol, had m. p. 130·5—131·5° (Found: C, 49·1; H, 2·7; N, 3·0; Cl, 33·3. $C_{17}H_{11}O_3NCl_4$ requires C, 48·7; H, 2·7; N, 3·3; Cl, 33·8%).

Reaction of Dimethyl αα′-Azoisobutyrate with Quinol.—A solution of dimethyl αα′-azoisobutyrate (30·8 g.) and quinol (33·55 g.) in ethanol (120 ml.) was heated under reflux for 6 hours. The solvent was removed by distillation and the residue, dissolved in ether, was extracted with a solution of sodium hydroxide (30 g.) and sodium suphite (5 g.) in water (300 ml.). On fractional distillation the ethereal solution yielded fractions, b. p. 215—230° (13·5 g., 51%), and 180—190°/27 mm. (5·5 g., 21%). Almost the same quantities were obtained when (I) was decomposed in benzene or phenol as solvents (Bickel and Waters, *loc. cit.*). The aqueous solution was acidified and extracted with ether, yielding quinol, m. p. 168—170° (32·48 g., 97%).

One of the authors (A. F. B.) is indebted to the Koninklijke Shell-Laboratorium, Amsterdam, for the opportunity to carry out this investigation.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, April 3rd*, 1950.]

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358. *Organic Phosphorus Insecticides. Part I. Synthesis of Bisdimethylaminophosphonous Anhydride containing* ^{32}P.

By J. E. GARDINER and B. A. KILBY.

A method is described for the conversion of radioactive phosphoric acid into phosphoryl chloride on a small scale, and thence through chlorobisdimethylaminophosphine oxide (I) into bisdimethylaminophosphonous anhydride (III) (cf. preliminary note, *Research*, 1949, **2**, 500). The labelled product (III) is suitable for tracer work in plants (in which the compound acts as a systemic insecticide) and in animals (where it shows anticholinesterase activity). Preparation of the non-radioactive form of (III) on a larger scale is also described.

THE discovery of systemic insecticides by Schrader and Kukenthal (B.I.O.S. Final Report No. 714 H.M.S.O., London, 1947) has opened up new possibilities for the control of insect pests. Certain compounds can be absorbed through the plant cuticle and transported in the sap-stream to render the whole plant poisonous to certain biting and sucking insects. The compounds can also be absorbed through the root system if the plants are watered with aqueous solutions. Among the compounds described by Schrader which displayed this systemic insecticidal action, bisdimethylaminophosphonous anhydride (III) appears to show the greatest promise as its mammalian toxicity is less than those of other systemic insecticides, and in addition, it displays a valuable selective action on insects, being highly toxic to aphides and relatively non-poisonous to beneficial insects (Ripper, Greenslade, and Lickerish, *Nature*, 1949, **163**, 787). If this insecticide is to be used on a significant scale, more information will be desirable on its entry into, transportation in, and disappearance from, plants and on its fate in animals. The radioactive tracer technique should be particularly useful in the biological investigation of these subjects, and we have therefore worked out a suitable method for the synthesis of (III) incorporating ^{32}P.

A method for the preparation of (III) indicated by Schrader *et al.* (but without experimental details) is to heat an equimolecular mixture of chlorobisdimethylaminophosphine oxide (I) and ethyl bisdimethylaminophosphonite (II) in boiling xylene:

Alternatively the corresponding sodium salt can be used in place of the ester (II). In the radioactive work, we employed the ester method for convenience of manipulation as the reaction mixture is homogeneous, stirring and filtration being avoided.

Two methods are available for the preparation of (I). In the first (Cook, Ilett, Saunders, Stacey, Watson, Wilding, and Woodcock, *J.*, 1949, 2921) phosphoryl chloride (1 mol.) is treated with anhydrous dimethylamine (4 mol.) in ether :

$$POCl_3 + 4NHMe_2 = (I) + 2NHMe_2,HCl$$

In the second the reaction is carried out in two stages; a single dimethylamino-group can be introduced by refluxing dimethylamine hydrochloride in excess of phosphoryl chloride (Michaelis, *Annalen*, 1903, **326**, 179), giving dichlorodimethylaminophosphine oxide, which is subsequently treated with two equivalents of dimethylamine in ether. The first method is very convenient when working on a small scale, and was used in the preparation of radioactive (II); but when a number of larger batches of non-radioactive (III) were being made, the second method was advantageous as the hydrochloride obtained as a by-product in the second stage was utilized in the first stage of the subsequent run. Compound (II) was prepared by reaction of (I) with sodium ethoxide.

Radio-phosphorus is supplied in the form of phosphoric acid and it is necessary to convert this into phosphoryl chloride. This may be achieved by the passage of carbonyl chloride (or a chlorine–carbon monoxide mixture) over heated metal phosphates (cf. Mellor, "Comprehensive Treatise of Inorganic and Theoretical Chemistry," Vol. VIII, p. 1020). Banks, Boursnell, Dewey, Francis, Tupper, and Wormall (*Biochem. J.*, 1948, **43**, 518) passed carbonyl chloride over heated calcium phosphate–charcoal to prepare radioactive phoshoryl chloride on a small scale. In this method, however, the calcium chloride formed as a by-product coated the unchanged calcium phosphate, necessitating removal of the mixture from the reaction vessel, regrinding, and reheating to complete the reaction. When, however, ferric phosphate (without charcoal) and carbonyl chloride are used (Andreau and du Pont, U.S.P. 1462732, 1923), all the products are volatile at the temperature of reaction and the ferric chloride can easily be condensed out by slight cooling. Yields of up to 93% were obtained in runs in which the theoretical yield was one gram. The sample of (III) obtained as described in the Experimental section had a specific activity of about 18 μc./g.

Experimental.

Dichlorodimethylaminophosphine Oxide.—Dimethylamine hydrochloride (638 g., recrystallised from ethanol and dried over phosphoric oxide *in vacuo*) and phosphoryl chloride (4·2 kg.; redistilled) were heated under reflux for 20 hours until evolution of hydrochloric acid had ceased and the hydrochloride was completely in solution. Fractionation through a Fenske column gave the product, b. p. 85—88°/15—18 mm. (1272 g., 94%) (Found : C, 15·3; H, 3·8; N, 8·6; Cl, 44·3. Calc. for $C_2H_6ONCl_2P$: C, 14·8; H, 3·7; N, 8·6; Cl, 43·8%). About 2·8 kg. of phosphoryl chloride were recovered.

Chlorobisdimethylaminophosphine Oxide.—(*a*) Dichlorodimethylaminophosphine oxide (340 g.) in dry ether (1·5 l.) was cooled in ice, and a solution of dimethylamine (190 g.) in ether (500 ml.) added during 90 minutes with stirring, which was continued overnight as the mixture warmed to room temperature. The precipitate of dimethylamine hydrochloride was removed and washed with ether (1 l.). Fractionation of the combined ethereal solution and washings yielded the product, b. p. 97—98°/4 mm. (299 g., 84%) (Found : C, 28·1; H, 6·9; N, 16·1; Cl, 21·4. Calc. for $C_4H_{12}ON_2ClP$: C, 28·2; H, 7·0; N, 14·3; Cl, 20·8%).

(*b*) Phosphoryl chloride (155 g.) in ether (1 l.) was cooled in ice, and dimethylamine (187·5 g.) in ether (500 ml.) added with stirring during 1 hour, and the whole left overnight. The solid hydrochloride was filtered off and washed with ether, and the filtrate fractionated. The product (112 g., 64%) had b. p. 97°/6 mm. (cf. Cook *et al.*, *loc. cit.*).

Ethyl Bisdimethylaminophosphonite.—Chlorobisdimethylaminophosphine oxide (341 g.) in ethanol (500 ml.) was added with stirring to a solution of sodium (46 g.) in ethanol (1500 ml.) during 20 minutes, and the mixture heated under reflux for a further 20 minutes. The precipitate of sodium chloride was removed, alcohol distilled off, and the residue fractionated *in vacuo*. The product (318 g., 88·5%) was collected from 93·5°/7 mm. to 95·5°/10 mm.

Bisdimethylaminophosphonous Anhydride.—Chlorobisdimethylaminophosphine oxide (68·2 g.) and ethyl bisdimethylaminophosphonite (72 g.) in xylene (300 ml.) were heated for 20 hours under reflux. Ethyl chloride was evolved. On distillation of the residue, the product was obtained as a colourless and almost odourless liquid, b. p. 110—112°/0·003 mm. (92·6 g., 81%), completely miscible with water (Found : C, 33·9; H, 8·5; N, 19·8. $C_8H_{24}O_3N_4P_2$ requires C, 33·6; H, 8·4; N, 19·6%). The b. p. varied slightly for different preparations, being rather dependent on the bath-temperature.

Radioactive Ferric Phosphate.—Active phosphoric acid solution (1140 μc. in 0·54 ml.) was washed out from its ampoule with phosphoric acid solution (20 ml. containing 31·92 g./l.) and water into a 100-ml. graduated flask. A sample (1 ml.) was withdrawn as a standard for radioactive assay, and the remainder was added slowly with vigorous stirring to a solution (50 ml.) of ferric acetate in acetic acid (8·25 g. of Fe and 120 ml. of acetic acid per litre). Solid ammonium acetate (5 g.) was then added and the mixture boiled for 5 minutes. The precipitate of ferric phosphate was removed by centrifuging, washed once with ethanol and twice with ether, dried at 120°, powdered with a glass rod, and transferred to a silica tube. After being heated to red heat for 90 minutes, the voluminous precipitate had shrunk to a third of its original volume. When cool, the granular powder was packed into a silica tube as shown in Fig. 1,

for use in the following preparation. Losses of radioactive material during precipitation and drying were less than 2%.

FIG. 1.

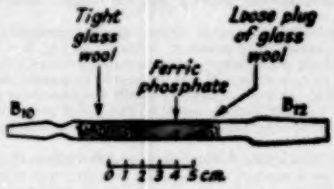
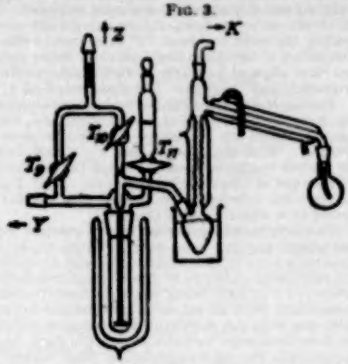
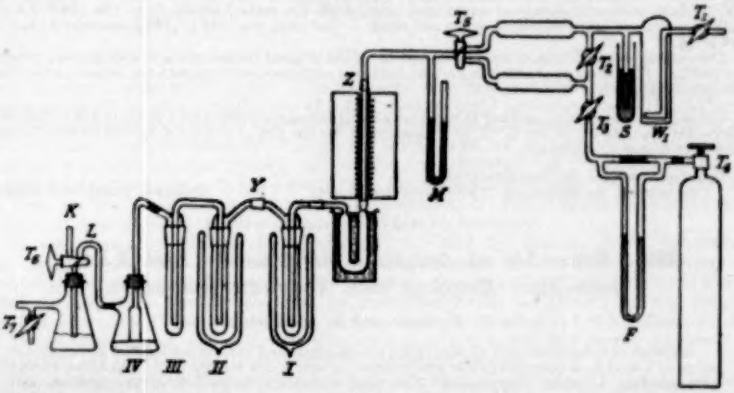


FIG. 3.



Radioactive Phosphoryl Chloride.—The apparatus used is shown diagramatically in Fig. 2. Dry nitrogen (or air), carbonyl chloride, or a mixture was admitted to the reaction vessel by adjustment of the stopcocks T_1 to T_5 (*S*, safety valve; W_1, wash-bottle containing concentrated sulphuric acid; *M*, mercury manometer; *F*, flowmeter). Carbonyl chloride was obtained from a cylinder connected with polyvinyl chloride tubing. From T_4 to trap III, the apparatus was constructed in short sections joined by standard ground-glass joints to give flexibility and to facilitate cleaning. The reaction vessel *Z* was a silica tube (10 cm. long, 1 cm. internal diameter) heated in a small electric tube furnace to 400—450°, and was followed by a U-tube packed with glass wool and maintained at 120—130° in a metal bath (to condense out ferric chloride). Traps I and II were jacketed and fitted with close-fitting brass shields

FIG. 2.



to prevent spilling of radioactive material in the event of accidental breakage. These traps were surrounded by solid carbon dioxide–alcohol. The product and excess of carbonyl chloride were collected in trap I, while II served as a safety trap against sucking back and also to remove any traces of product not condensed by I. Any carbonyl chloride remaining in the gas stream was removed by trap III containing water, and by trap IV containing soda-lime. Waste gas was passed through T_4 into a bubbler, past an air leak (controlled by T_7) into a water-pump. During operation, the apparatus was at all times run with a slight negative pressure to avoid any escape of volatile radioactive material.

After the packed reaction tube had been fitted, the heating units were switched on and the apparatus was dried out by a stream of dry nitrogen or air, the stopcocks being adjusted so that the manometer *M* showed a negative pressure of about 8 cm. Hg. When dry, the cooling baths were fitted and a slow stream of carbonyl chloride mixed with air was admitted. As reaction proceeded, the air supply was stopped and the carbonyl chloride stream increased. About 50 ml. of liquid carbonyl chloride were

collected during 6 hours (coarseness of control of T_4 prevented a slower rate of flow). The carbonyl chloride stream was then stopped and the apparatus swept out with air. The tube of trap I was removed and connected to a simple stillhead. Most of the carbonyl chloride was then allowed to boil off slowly at room temperature (air-jacket around the tube), and the final traces were removed by heating the tube to about 75° in a water-bath. The receiver-tube was then cooled in liquid air, the distillation of the phosphoryl chloride being completed by evacuation for a short time. The apparatus was then allowed to warm to room temperature, dry air admitted, and the receiver rapidly removed, stoppered, and weighed. The yield was 0·93 g. (93%).

Radioactive Chlorobisdimethylaminophosphine Oxide.—The apparatus shown diagrammatically in Fig. 3 was fitted in place of the reaction tube, traps, etc., between the points *K*, *Y*, and *Z* in Fig. 2. The reaction vessel for this stage was the receiver into which phosphoryl chloride had previously been distilled. With T_{10} open, T_9 and T_{11} closed, and T_8 set to *L*, a stream of nitrogen could be passed down the narrow centre tube and through the sintered-glass disc (10-mm. diameter) to stir the reactants and then escape through the trap system. With T_{10} closed, T_9 open, and T_8 set to *K*, the liquid contents of the reaction tube could be filtered into the flask of a micro-fractionating apparatus which was being heated in a water-bath to about 50°.

To the tube containing the known amount of phosphoryl chloride (0·93 g.), sodium-dried ether (10 ml.) was added and the tube quickly fitted to the apparatus described above. The solution was stirred vigorously by a stream of nitrogen, and the reaction vessel then cooled in solid carbon dioxide–alcohol. The calculated quantity of dimethylamine solution in ether (10% w/v; 10·5 ml., 4 mols.) was then added slowly *via* T_{11}, care being taken to keep the reactants always well stirred. The tap-funnel was then washed out with 10 ml. of ether, and the apparatus allowed to warm to room temperature and left overnight with gas stirring. The reaction vessel was then again cooled (to reduce the solubility of the dimethylamine hydrochloride), the taps were adjusted as described above, and the mixture was filtered into the micro-distillation flask where the ether distilled off. The solid hydrochloride, well cooled, was washed 3 times with cold dry ether. When the crude product had been transferred in this manner to the distillation flask, this was set for fractionation, glass wool being added to prevent bumping. Inert chlorobisdimethylaminophosphine oxide (*ca.* 7 g. in 2 portions) was added at this stage as a diluent, and distillations carried out at a low pressure, the flask being heated in a stirred oil-bath. The fractions, b. p. 62—64°/1—1·1 mm. (bath-temp. 82—84°), were collected and weighed (7·2 g.). A small sample was taken for radioactive assay and showed a yield of 42·7% calculated on ^{32}P content of the original 99 ml. of phosphoric acid solution.

Radioactive Bisdimethylaminophosphorous Anhydride.—Active chlorobisdimethylaminophosphine oxide (7·2 g.) from the previous experiment was washed with dry benzene (15 ml.) into a 50-ml. flask, ethyl bisdimethylaminophosphonite (10 g., slight excess) added, and the mixture heated overnight under reflux in a stirred oil-bath at 130—145°, moisture being excluded by a calcium chloride tube. The mixture was then distilled through a short Vigreux column. A small first fraction distilling up to 128°/1·5 mm. consisted mainly of unchanged ester, while the main fraction, b. p. 139—140°/1·5 mm. (bath temperature 160°), consisted of the anhydride. The yield was 9·44 g. (78%) and specific activity 18·4 μc./g.

The overall yield, calculated from the activities of the original phosphoric acid and the final product, was 19·9%. (The glass wool added to prevent bumping on the above fractionations retained appreciable amounts of radioactive material.)

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359. *Researches on Acetylenic Compounds. Part XXIV. Diels–Alder Reactions with Acetylenic Keto-esters.*

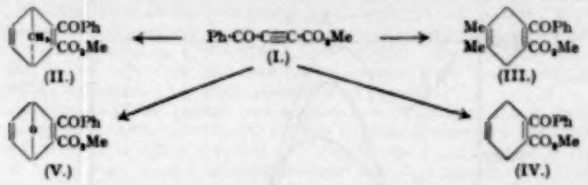
By T. Y. Shen and M. C. Whiting.

Addition reactions between $\alpha\beta$-acetylenic γ-keto-esters and various conjugated dienes give a series of 2-acyl-3 : 6-dihydrobenzoic esters, some of which are readily dehydrogenated to the corresponding aromatic compounds. The light-absorption properties of the adducts are compared with those of analogous adducts obtained from ethynyl ketones, and with those of acylbenzoic esters.

In Part III of the present series (Bowden and Jones, *J.*, 1946, 52) the application of the Diels–Alder reaction to ethynyl ketones was described. It was to be expected that the recently available $\alpha\beta$-acetylenic γ-keto-esters (Nineham and Raphael, *J.*, 1949, 118; Jones, Shen, and Whiting, *J.*, 1950, 236) would undergo similar diene additions and, because of possible applications of the method to the synthesis of fused-ring systems, and the interest aroused by the anomalous light-absorption properties of the adducts obtained from ethynyl ketones, this reaction has been examined.

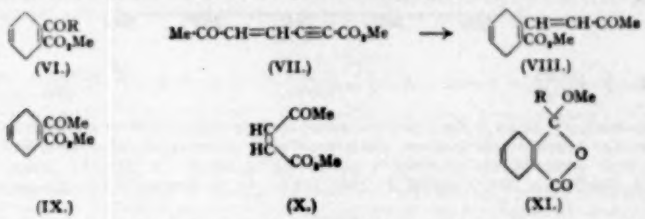
The acetylenic keto-esters proved rather more reactive as dienophils than the corresponding

ethynyl ketones, but their lower stability made the reaction conditions more critical. Thus methyl benzoylpropiolate (I) combined smoothly with *cyclo*pentadiene and 2 : 3-dimethylbutadiene, at room temperature and *ca.* 70° respectively, to give the adducts (II) and (III) in



good yields. The reaction with butadiene, however, required very careful temperature control. At 20° very little reaction took place during seven days even when an excess of the hydrocarbon was used as solvent, but in an autoclave at 45° a good yield of (IV) was obtained after 6—18 hours. On the other hand heating to 60° resulted in the formation of a dark, uncrystallisable product from which only methyl *o*-benzoylbenzoate could be isolated on distillation. Similar difficulties were encountered in the reaction with furan, a fair yield of the adduct (V) being obtained when the reaction temperature was 50°.

Reactions between butadiene and the aliphatic keto-esters, methyl β-acetyl- and β-butyrylpropiolates, were next examined. The expected adducts (VI; R = Me and Pr respectively)



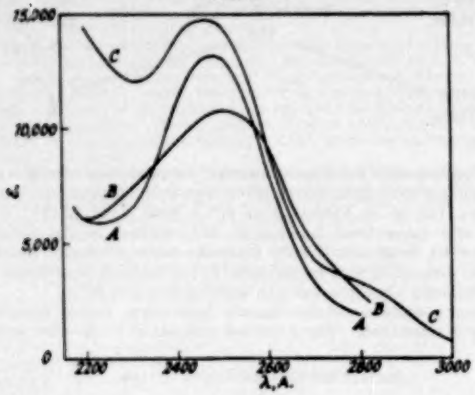
were obtained in good yields at 50°. The vinylacetylenic keto-ester (VII) also combined with butadiene at 50° to give a small yield of a high-boiling liquid formulated as (VIII), although analytical data indicated that it was not pure. Its light-absorption (see below) resembled that of a typical doubly-unsaturated conjugated ketone and its 2 : 4-dinitrophenylhydrazone analysed well, after chromatographic purification, for a derivative of (VIII) and showed the expected light-absorption. It has already been found (Bowden, Braude, Jones, and Weedon, *J.*, 1945, 45) that hex-3-en-5-yn-2-one gives amine-adducts in which only the acetylenic linkage is involved, and therefore the formation of (VIII) is not unexpected.

It was shown by Bowden and Jones (*loc. cit.*) and by Braude, Jones, Sondheimer, and Toogood (*J.*, 1949, 607) that 2 : 5-dihydroacetophenone and analogous substances are converted into the corresponding aromatic ketones by a variety of oxidising agents and also by heating to *ca.* 175°. Similar behaviour was encountered with the present series of dihydrobenzene derivatives. Thermal dehydrogenation obviously occurred in the butadiene reaction at 60° described above, and oxidation with chromic acid in acetic acid readily converted the esters (III) and (IV) into the corresponding benzenoid compounds.

The adducts derived from methyl β-benzoylpropiolate closely resemble acetophenone in their light-absorption properties and these are not very different from those of the *o*-benzoylbenzoic esters which have been examined (*e.g.*, see Fig. 1). It is probable that the absorption of the benzoyl group is predominant in these cases. On the other hand, the spectra of the adducts (VI; R = Me or Pr) from butadiene and methyl β-acetyl- and β-butyryl-propiolates (the curves for these two substances almost coincide) are quite different from that of methyl acetophenone-*o*-carboxylate (Fig. 2); indeed the intensity of absorption in the former cases is so low that it was at first considered possible that these esters had a cyclic structure such as (XI). This hypothesis was supported by the fact that they failed to form 2 : 4-dinitrophenylhydrazones, even under the drastic conditions necessary for the preparation of these derivatives from the benzoyldihydrobenzoic esters. Further consideration of the light-absorption data,

however, reveals that these are not incompatible with the structures assigned. 2 : 5-Dihydroacetophenone has already been found by Bowden and Jones (*J.*, 1946, 52; cf. Braude, Jones, Sondheimer, and Toogood, *J.*, 1949, 607) to exhibit abnormally low intensity light-absorption,

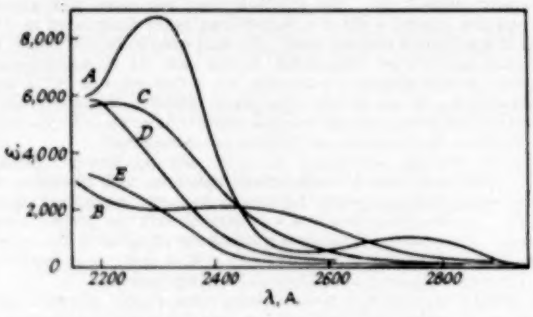
FIG. 1.



A. *B.* *C.*

and a carbomethoxyl group in the *o*-position would be expected to produce a further reduction in intensity by virtue of its steric effect, which would tend to prevent the αβ-unsaturated ketone grouping from assuming its preferred coplanar configuration (cf. Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890). In the absence of through-conjugation

FIG. 2.



A. *B.* *C.* *D.* *E.*

(see below) the carbomethoxyl group might lead to a hypsochromic displacement of the maximum, and a combination of these effects might well result in absorption such as is indicated in curve *B* (Fig. 2). This reasoning was tested in the following manner. It was shown by Braude, Jones, Sondheimer, and Toogood (*loc. cit.*) that 2 : 5-dihydroacetophenone could be

converted, by partial hydrogenation of the isolated double bond, into 1-acetyl*cyclo*hexene which showed no light-absorption abnormalities. Partial hydrogenation of the keto-ester (VI; R = Me) gave an apparently homogeneous product (IX) which showed much more intense absorption (*C*; Fig. 2) than did the parent compound (VI; R = Me); the other effects mentioned above are still apparent, however, in that the intensity is still appreciably lower than that of acetyl*cyclo*hexene ($\lambda_{max.}$ 2320—2330 A., ε = 13,500). The two cases thus appear to be analogous and it is clear that the keto-ester has the normal rather than the cyclic structure, as would indeed by expected in view of the method of preparation.

In order to make available another *cis*-β-acylacrylic ester having an unambiguous structure, the parent compound, methyl *cis*-β-acetylacrylate (X) was prepared by semihydrogenation of the acetylenic ester. Its light-absorption (*D*; Fig. 2) was similar to that of (IX), the latter absorbing at longer wave-lengths, as expected from the alkyl substitution of ethylenic bond. The acetylenic ester itself showed similar but less intense absorption (*E*; Fig. 2) (cf. methyl vinyl and methyl ethynyl ketones; Bowden, Heilbron, Jones, and Weedon, *J.*, 1945, 39). The results obtained for the various γ-keto-αβ-unsaturated esters are thus consistent; they show that the system is cross-conjugated, as would be expected in view of the opposed polarities of the keto- and carbomethoxyl groups and by analogy with maleic and fumaric esters ($\lambda_{max.}$ 1927 and 2087 A., log ε = 4·34 and 4·32 respectively; Sörensen, *Annalen*, 1941, **546**, 57) and with pyruvic ester ($\lambda_{max.}$ 3287 A., log ε = 0·73, and end absorption with log ε = 2·88 at 2144 A.; Bielecki and Henri, *Ber.*, 1914, **47**, 1690). Nevertheless it must be borne in mind that in all the cases examined the double bond had a *cis*-configuration and " through " conjugation would in any case be hindered sterically. Further work on the light-absorption of γ-keto-acids and -esters in connection with their tautomeric behaviour is in progress in these laboratories.

Experimental.

(Light-absorption data were determined using alcohol as solvent with a Beckman Model B spectrophotometer.)

Methyl 2-Benzoyl-3 : 6-dihydrobenzoate (IV).—A mixture of methyl benzoylpropiolate (Nineham and Raphael, *loc. cit.*) (3 g.), butadiene (2 c.c.), and a trace of quinol was heated in a small steel autoclave (capacity 50 c.c.) at 45° for 18 hours. After cooling and removal of excess of butadiene the residue solidified, and crystallisation from light petroleum (b. p. 40—60°) gave the *keto*-ester (3·1 g.) as rhombic prisms, m. p. 65° (Found: C, 74·55; H, 5·75; $C_{14}H_{14}O_3$ requires C, 74·35; H, 5·8%). The 2 : 4-*dinitrophenylhydrazone*, prepared by refluxing the compound with methanolic 2 : 4-dinitrophenylhydrazine sulphate solution for 12 hours, separated from ethyl acetate–ethanol in red prismatic needles, m. p. 208° (Found: C, 60·0; H, 4·45. $C_{20}H_{18}O_6N_4$ requires C, 59·7; H, 4·3%).

Methyl 2-Benzoyl-4 : 5-dimethyl-3 : 6-dihydrobenzoate (III).—A mixture of methyl benzoylpropiolate (3 g.) and 2 : 3-dimethylbutadiene (2·5 g.) was heated under reflux for 18 hours. Crystallisation of the resultant solid from benzene–light petroleum (b. p. 40—60°) gave the *keto*-ester as prisms, m. p. 103—104° (Found: C, 75·25; H, 6·75. $C_{15}H_{16}O_3$ requires C, 75·55; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone*, obtained by interaction with methanolic 2 : 4-dinitrophenylhydrazine sulphate for 4 days at room temperature, crystallised from ethyl acetate–ethanol in orange-red flat needles, m. p. 224—226° (decomp.) (Found: C, 61·0; H, 4·9. $C_{21}H_{20}O_6N_4$ requires C, 61·2; H, 4·95%).

Methyl 2-Benzoyl-3 : 6-endomethylene-3 : 6-dihydrobenzoate (II).—*cyclo*Pentadiene (2 g.; freshly redistilled) was added to methyl benzoylpropiolate (2 g.), and the resultant exothermic reaction was moderated by external cooling. After a few minutes at room temperature removal of excess of diene and distillation at 85—90° (bath temp.)/10^{-4} mm. gave the *keto*-ester (2·3 g.) as a light-yellow, very viscous liquid, n_D^{18} 1·5686 (Found: C, 75·55; H, 5·65. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·55%). The 2 : 4-*dinitrophenylhydrazone*, formed comparatively readily, crystallised from ethyl acetate–ethanol in orange-red rhombic plates, m. p. 207° (Found: C, 60·75; H, 4·2. $C_{22}H_{18}O_6N_4$ requires C, 60·8; H, 4·2%).

Methyl 3 : 6-endo-Oxido-2-benzoyl-3 : 6-dihydrobenzoate (V).—A mixture of methyl benzoylpropiolate (3 g.) and furan (1·5 g.) was heated in a small autoclave to 50° for 6 hours. Distillation of the resultant dark syrup after the removal of more volatile material gave the *keto*-ester (1·6 g.), b. p. 80° (bath temp.)/10^{-4} mm., n_D^{20} 1·5666 (Found: C, 70·05; H, 4·75. $C_{14}H_{12}O_4$ requires C, 70·5; H, 4·7%). The 2 : 4-dinitrophenylhydrazone, m. p. 178°, could not be obtained analytically pure.

Methyl 2-Acetyl-3 : 6-dihydrobenzoate (VI; R = Me).—A mixture of methyl acetylpropiolate (Jones, Shen, and Whiting, *loc. cit.*) (2 g.), butadiene (2 c.c.) and a trace of quinol was heated in a small autoclave to 50° for 18 hours. After the removal of excess of diene distillation gave the *keto*-ester as a liquid, b. p. 81—82°/0·02 mm., n_D^{18} 1·5008, which when kept solidified and had m. p. 32° (Found: C, 66·95; H, 7·05. $C_{10}H_{14}O_3$ requires C, 66·65; H, 6·7%). It did not form a 2 : 4-dinitrophenylhydrazone even under vigorous conditions.

Methyl 2-Butyryl-3 : 6-dihydrobenzoate (VI; R = Pr^n).—A mixture of methyl butyrylpropiolate (Jones, Shen, and Whiting, *loc. cit.*) (1·1 g.) and butadiene (1 c.c.) was heated in a small autoclave at 50° for 18 hours. After removal of excess of diene and cooling, the residue solidified, and crystallisation from light petroleum (b. p. 40—60°) gave the *keto*-ester (1·0 g.) as needles, m. p. 55° (Found: C, 69·45; H, 7·75. $C_{12}H_{18}O_3$ requires C, 69·2; H, 7·8%). It did not form a 2 : 4-dinitrophenylhydrazone even under drastic conditions.

4-(2-Carbomethoxy-3 : 6-dihydrophenyl)but-4-en-2-one.—A mixture of methyl 5-ketohex-3-en-1-yne-

1-carboxylate (Jones, Shen, and Whiting, *loc. cit.*) (1·0 g.) butadiene (1 c.c.), and a trace of quinol was heated in a small autoclave at 50° for 6 hours. Removal of the excess of diene, followed by distillation at 80—100° (bath temp.)/10^{-4} mm., gave the crude *keto*-ester (0·4 g.) as an oil, n_D^{25} 1·5206 (Found: C, 67·8; H, 6·65. $C_{13}H_{14}O_3$ requires C, 69·9; H, 6·85%). Light absorption: Maximum, 2810 A.; ε = 9,500. As insufficient material was available for purification it was converted into its 2 : 4-*dinitrophenylhydrazone* which, after chromatography and crystallisation from ethyl acetate, formed red prismatic needles, m. p. 186° (Found: C, 58·25; H, 4·95. $C_{19}H_{18}O_6N_4$ requires C, 55·95; H, 4·7%). Light absorption: Maxima, 2560, 3080 and 3950 A.; ε = 14,500, 11,500, and 32,500 respectively.

o-Benzoylbenzoic Acid.—Methyl 2-benzoyl-3 : 6-dihydrobenzoate (0·5 g.) was dissolved in glacial acetic acid (20 c.c.) and treated with 6N-chromic acid (1·0 c.c.). Isolation with ether followed by hydrolysis with aqueous-methanolic potassium hydroxide solution at room temperature gave *o*-benzoylbenzoic acid (0·35 g.), m. p. 126°, undepressed on admixture with an authentic specimen.

An attempted dehydrogenation with chromic acid in acetone (Braude, Jones, Sondheimer, and Toogood, *loc. cit.*) gave a heterogeneous product.

2-Benzoyl-4 : 5-dimethylbenzoic Acid and Methyl Ester.—A solution of the corresponding dihydro-ester (1·1 g.) in glacial acetic acid (30 c.c.) was treated with 6N-chromic acid (1·8 c.c.) added slowly. Dilution with water gave a precipitate which was crystallised from light petroleum (b. p. 40—60°) to give the keto-ester (1·0 g.) as rhombic prisms, m. p. 124° (Found: C, 75·8; H, 5·85. Calc. for $C_{17}H_{16}O_3$: C, 76·1; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange-yellow plates, m. p. 249° (Found: C, 61·4; H, 4·35. $C_{23}H_{20}O_6N_4$ requires C, 61·6; H, 4·5%). Hydrolysis of the ester (0·15 g.) with methanolic potassium hydroxide gave the acid (0·1 g.), which after crystallisation from benzene–light petroleum (b. p. 40—60°) formed plates, m. p. 197° (Found: C, 75·55; H, 5·9. Calc. for $C_{17}H_{16}O_3$: C, 75·6; H, 5·55%) (Fieser and Fieser, *J. Amer. Chem. Soc.*, 1935, **57**, 1679 give m. p. 123·5° and 197·5° for the methyl ester and the acid, respectively).

Methyl 2-Acetylcyclohexene-1-carboxylate.—A solution of methyl 2-acetyl-3 : 6-dihydrobenzoate (2·0 g.) in methyl acetate (25 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (10%; 75 mg.). When the theoretical amount of hydrogen had been absorbed (278 c.c. at 22°/755 mm.) the catalyst was separated and the solvent removed under reduced pressure at room temperature. Distillation of the residue gave *methyl 2-acetylcyclohexene-1-carboxylate* (1·3 g.), b. p. 110—112°/2 mm., n_D^{25} 1·4834 (Found: C, 66·3; H, 7·75. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%).

Methyl cis-β-Acetylacrylate.—A solution of methyl acetylpropiolate (2·0 g.) in methyl acetate (25 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (50 mg.; 10%). When the theoretical amount of hydrogen had been absorbed (400 c.c. at 762 mm./23°) the catalyst was filtered off and the solvent removed under reduced pressure at room temperature. Distillation of the residue gave *methyl cis-β-acetylacrylate* (1·1 g.), b. p. 85°/22 mm., n_D^{25} 1·4390.

It readily formed a 2 : 4-*dinitrophenylhydrazone* which, after chromatographic purification on alumina and recrystallisation from benzene–light petroleum (b. p. 60—80°), formed orange-yellow plates, m. p. 195° (Found: C, 53·95; H, 3·65. $C_{12}H_{12}O_6N_4$ requires C, 53·6; H, 3·95%).

The authors express their gratitude to Professor E. R. H. Jones, F.R.S., for his valuable advice. They also thank Mr. E. S. Morton for microanalyses and Miss E. Fuller for light-absorption determinations. One of them (T. Y. S.) is indebted to the Chinese Government for a Research Scholarship.

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360. *A New Route to the Phthalide-isoquinoline Bases, and a Synthesis of (−)-Hydrastine.*

By Robert D. Haworth and A. Reginald Pinder.

A new method for the synthesis of alkaloids of the hydrastine type has been developed. The racemic bases, hydrastine-*a* and -*b*, obtained previously by another method by Hope, Pyman, Remfry, and Robinson (*J.*, 1931, 236) have been prepared, and hydrastine-*a* has been resolved into (+)- and (−)-forms, the latter of which was identical with (−)-hydrastine from natural sources.

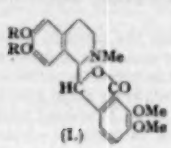
Similar reactions led to the synthesis of two racemic modifications of cordrastine, but attempts to resolve the bases into their optically active forms have been unsuccessful.

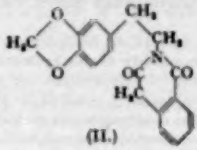
The synthetic approach to the lactonic 1-benzyl*iso*quinoline alkaloids of type (I) is confined to the method of Perkin and Robinson (*J.*, 1911, **99**, 775) (see also Hope and Robinson, *J.*, 1911, **99**, 1153) in which an *iso*quinoline ϕ-base is condensed with a phthalide or its nitro- or iodo-derivative. In this way (±)-narcotine and (±)-*iso*narcotine (α- and β-gnoscopine) were prepared and the former was resolved into its optically active forms (Perkin and Robinson, *loc. cit.*, p. 788); later two inactive modifications of hydrastine (I; RR = CH_2) known as hydrastine-*a* and -*b* were synthesised (Hope, Pyman, Remfry, and Robinson, *J.*, 1931, 236) but resolution was not effected.

The isolation of several new alkaloids of type (I), including bicuculline from *Dicentra cucullaria*, etc. (Manske, *Canadian J. Res.*, 1938, **8**, 142), adlumine from *Adlumia fungosa*

(Manske, *ibid.*, p. 404), cordrastine (I; R = Me) from *Corydalis aurea* (Manske, *ibid.*, 1938, **16**, *B*, 81) and others (Manske, *ibid.*, 1933, **8**, 210, 404; 1936, **14**, *B*, 325, 347, 354) has revived interest in this field, and the ϕ-base-phthalide reactions have been employed to synthesise (±)-bicuculline (Groenewoud and Robinson, *J.*, 1936, 199).

The present communication describes an alternative series of reactions which have been developed for the synthesis of alkaloids of type (I). During some preliminary experiments a detailed examination of the properties of *N*-(2-3′ : 4′-methylenedioxyphenylethyl)homophthalimide (II) showed that the amic acid, m. p. 158—159°, described by the previous workers


(I.)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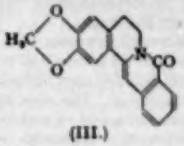
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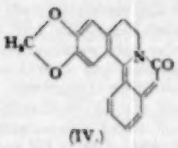
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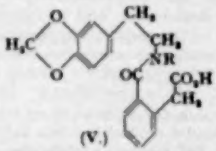
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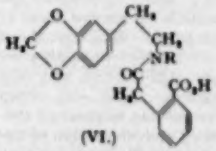
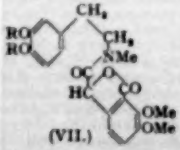
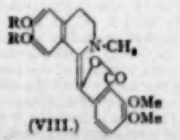

(VI.)

(Haworth, Perkin, and Pink, *J.*, 1925, **127**, 1718) was impure, and that, in fact, alkaline hydrolysis of the imide (II) yielded a mixture of two isomeric *amic acids*, m. p. 163° and 154° respectively. The higher-melting acid gave a *methyl* ester, m. p. 96°, and the lower-melting acid a *methyl* ester, which existed in a labile form, m. p. 93·5°, and a stable form, m. p. 128°. When 2-3′ : 4′-methylenedioxyphenylethylamine was condensed with homophthalic anhydride in benzene solution, the amic acid, m. p. 154°, was obtained in high yield, and the isomeric acid was not isolated. Heating either of the amic acids yielded the imide (II), but the methyl esters showed a different behaviour when treated with phosphorus oxychloride in toluene solution; the ester, m. p. 128°, gave 2 : 3-methylenedioxyoxyprotoberberine (III), m. p. 180°, and the ester, m. p. 96°, gave the orange-red 2 : 3-methylenedioxyoxy*iso*protoberberine (IV), m. p. 225° (cf. Haworth, Perkin and Pink, *loc. cit.*). It is therefore probable that the amic acids, m. p. 163° and 154°, have the structures (V) and (VI) (R = H) respectively, and these conclusions are supported by measurements of the dissociation constants of the two acids. Wegscheider's observations (*Monatsh.*, 1903, **24**, 930) on the relative strengths of the carboxyl groups in homophthalic acid suggest that the acid (VI) should be stronger than (V), and we find that the acid, m. p. 154°, with $K = 1{\cdot}9 \times 10^{-4}$ is stronger than the acid, m. p. 163°, which has $K = 6{\cdot}3 \times 10^{-4}$.

Condensation of homophthalic anhydride and *N*-methyl-2-3′ : 4′-methylenedioxyphenylethylamine gave an amic acid, m. p. 151·5°, probably N-*methyl*-N-2-3′ : 4′-*methylenedioxyphenylethyl-o-carboxyphenylacetamide* (VI; R = Me), but attempts to cyclise this acid or the corresponding *methyl* ester, m. p. 88°, with phosphorus oxychloride or pentachloride, or phosphoric oxide, failed to yield any basic material and the reactions were abandoned.

A modification of the method used by Perkin, Rây, and Robinson (*J.*, 1925, **127**, 741) for the synthesis of oxyberberine has been developed into a general method for the synthesis of bases of type (I). Meconine-α-carboxyl chloride (Perkin, Rây, and Robinson, *loc. cit.*) and


(VII.)


(VIII.)

N-methyl-2-3′ : 4′-methylenedioxyphenylethylamine reacted readily in benzene to give N-*methyl*-N-(2-3′ : 4′-*methylenedioxyphenylethyl*)*meconine-α-carboxyamide* (VII; RR = CH_2), m. p. 137°,

which was converted in 50—55% yield into *dehydrohydrastine* (VIII; RR = CH_2), m. p. 205°, by the action of phosphorus oxychloride. This orange-red compound (VIII) was soluble in warm dilute hydrochloric acid, but when the solution was boiled decomposition gradually occurred and oxyhydrastinine and meconine were produced. Dehydrohydrastine was rapidly reduced in acetic acid solution in the presence of a platinic oxide catalyst to a mixture of two isomeric forms of hydrastine (I; RR = CH_2) which were separated by taking advantage of the differing solubilites of their respective *picrates* in acetone. The acetone-insoluble salt yielded hydrastine-*a*, m. p. 139°, and the soluble salt gave hydrastine-*b*, m. p. 152°, and the bases gave no depression of the melting points when mixed with samples kindly supplied by Sir Robert Robinson.

Marshall, Pyman, and Robinson (*J.*, 1934, 1315) failed to resolve the racemic hydrastine bases, but as a result of a comparative study of the epimerisation of narcotine and hydrastine they concluded that naturally occurring (−)-hydrastine was probably an optically active form of hydrastine-*a*. The new synthesis has made it possible to prepare relatively large amounts of hydrastine-*a* and -*b* and to subject the diastereoisomeric bases to a series of careful resolution experiments. Although we have converted hydrastine-*b* into the hydrogen (+)-tartrate, (+)- and (−)-*camphor*-10-*sulphonate*, and (+)-*bromocamphor*-10-*sulphonate*, it has not been possible to resolve these crystalline derivatives, and (±)-hydrastine-*b* was recovered from all fractions. Similarly the *hydrogen* (+)-*tartrate* of hydrastine-*a* resisted resolution but the (+)-*camphor*-10-*sulphonate* was separated by crystallisation from water into needles, m. p. 120—122°, which had $[\alpha]_D^{18} = -25{\cdot}5°$ unchanged by further crystallisation, and a semi-solid fraction which was obtained from the mother-liquors. The needles were apparently an inseparable mixture of the (+)-camphor-10-sulphonates of the (±)- and the (+)-hydrastine-*a* base; decomposition of the salt yielded a crude base with $[\alpha]_D^{16} = +26{\cdot}7°$ which was separated by crystallisation from methyl alcohol into (±)-hydrastine-*a*, m. p. 138—139°, $[\alpha]_D^{18} = 0°$, and (+)-*hydrastine*-a, m. p. 131—132° $[\alpha]_D^{18} = +42{\cdot}2°$. The semi-solid fraction from the mother-liquors from the (+)-camphor-10-sulphonate gave a crude base with $[\alpha]_D^{18} = -30{\cdot}2°$, which yielded (−)-*hydrastine*-a, m. p. 131—132°, $[\alpha]_D^{16} = -42{\cdot}1°$, on crystallisation from methyl alcohol. This base was identical with a specimen of (−)-hydrastine, kindly supplied by Messrs. T. & H. Smith of Edinburgh, which had $[\alpha]_D^{4} = -41{\cdot}7°$ and did not depress the melting point of the synthetic (−)-base.

Structure (I; R = Me) has been suggested for cordrastine, and two racemic modifications for this base have been synthesised by methods similar to those used in the synthesis of hydrastine-*a* and -*b*. *N*-Methyl-2-3′:4′-dimethoxyphenylethylamine reacted with meconine-*a*-carboxyl chloride, giving the *amide* (VII; R = Me), which was converted by the action of phosphorus oxychloride into *dehydrocordrastine* (VIII; R = Me). This yellow base was reduced catalytically to a mixture of two racemic modifications, cordrastine I, m. p. 155—156°, and cordrastine II, m. p. 118—119°. Cordrastine I, which was sparingly soluble in methyl or ethyl alcohol, gave crystalline (+)- and (−)-*camphor*-10-*sulphonates* and a crystalline (+)-*bromocamphorsulphonate*, but attempts to resolve these were unsuccessful. Of the salts with optically active acids, only the *hydrogen* (−)-*tartrate* of cordrastine II, m. p. 118—119°, was crystalline, and attempts to resolve this salt were unsuccessful.

Experimental.

Hydrolysis of N-(2-3′:4′-*Methylenedioxyphenylethyl*)*homophthalimide* (II).—This imide (4 g.) was prepared and hydrolysed as described by Haworth, Perkin, and Pink (*loc. cit.*). The crude amic acid was separated by fractional crystallisation from methyl alcohol into *o-carboxymethyl*-N-(2-3′:4′-*methylenedioxyphenylethyl*)*benzamide* (V; R = H) (1·8 g.), m. p. 163—164° (Found: equiv., 326·5; C, 66·4; H, 5·0%. $C_{18}H_{17}O_5N$ requires equiv., 327; C, 66·1; H, 5·2%), and N-(2-3′:4′-*methylenedioxyphenylethyl*)-*o-carboxyphenylacetamide* (VI; R = H) (1·7 g.), glistening needles, m. p. 153° (Found: C, 65·4; H, 5·4%; equiv., 326·8. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2%; equiv., 327).

Esterification of the silver salts with methyl iodide in ethereal suspension yielded the methyl esters. The *methyl* ester of (V; R = H) crystallised from ether in glistening colourless needles, m. p. 95—96° (Found: C, 66·7; H, 5·7. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·6%). The *methyl* ester of (VI; R = H) separated from methyl alcohol as prismatic needles, m. p. 93·5° (Found: C, 66·7; H, 5·7. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·8%), or long feathery needles, m. p. 128° (Found: C, 66·7; H, 5·8%); inoculation of a methyl-alcoholic solution of the lower-melting modification with the form of m. p. 128° resulted in the conversion of the former into the latter, but the reverse change was not realised.

Condensation of 2-3′:4′-*Methylenedioxyphenylethylamine and Homophthalic Anhydride.*—A mixture of the amine (0·5 g.) and the anhydride (0·5 g.) was refluxed in dry benzene (8 c.c.) for 2 hours during which a crystalline solid gradually separated. The cooled mixture was shaken with 5% sodium hydroxide solution (20 c.c.), and the alkaline extract was acidified; the crude acid, which slowly solidified, crystallised from methyl alcohol in glistening prismatic needles (0·9 g.), m. p. 152—153°, identical with the amic acid (VI; R = H) described above.

Cyclisation of the Methyl Esters, M. p. 128° and 95—96°.—The ester, m. p. 128° (0·5 g.), dry toluene (3·5 c.c.) and phosphorus oxychloride (1·25 c.c.) were gently refluxed for 45 minutes. The toluene and oxychloride were removed under reduced pressure and the residue was taken up with chloroform. The product crystallised from methyl alcohol in colourless needles, m. p. 180°, which gave no depression in m. p. with 2 : 3-methylenedioxyoxyprotoberberine (III).

The ester, m. p. 95°, underwent cyclisation more slowly; after 2 hours' refluxing the product, isolated as described above, crystallised from dilute acetic acid in orange-red needles, m. p. 225°, which gave no depression in m. p. with 2 : 3-methylenedioxyoxyisoprotoberberine (IV).

N-Methyl-N-(2-3′ : 4′-methylenedioxyphenylethyl)-o-carboxyphenylacetamide (VI; R = Me).—A benzene solution (20 c.c.) of *N*-methyl-2-3′ : 4′-methylenedioxyphenylethylamine (2·0 g.) and homophthalic anhydride (1·6 g.) was refluxed for 1½ hours. The cooled mixture was extracted with 5% sodium hydroxide solution (50 c.c.), and the *amic acid* (VI; R = Me) was recovered and crystallised from methyl alcohol; glistening white plates (3·7 g.), m. p. 151·5° (Found: C, 66·6; H, 5·6. $C_{19}H_{19}O_5N$ requires C, 66·8; H, 5·6%), were obtained. The *methyl* ester, prepared from the silver salt, crystallised from ether in colourless prisms, m. p. 88° (Found: C, 67·6; H, 5·8. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 5·9%).

N-Methyl-N-(2-3′ : 4′-methylenedioxyphenylethyl)meconine-a-carboxyamide (VII; RR = CH_2).—Meconine-a-carboxyl chloride (prepared from 10 g. of the corresponding acid as described by Perkin, Ray, and Robinson, *loc. cit.*) in benzene (25 c.c.) was added drop-wise and with cooling to a mixture of *N*-methyl-*N*-2-3′ : 4′-methylenedioxyphenylethylamine (8·0 g.) in benzene (20 c.c.) and N-sodium hydroxide solution (50 c.c.). The mixture was shaken for 3 hours, and after 12 hours the *amide* (VII; R = CH_2) which gradually separated was collected, washed with water, and crystallised from methyl alcohol. Elongated colourless prisms (12 g.), m. p. 136—137° (Found: C, 63·0; H, 5·5. $C_{21}H_{21}O_7N$ requires C, 63·2; H, 5·3%), were obtained.

Dehydrohydrastine (VIII; RR = CH_2).—The amide (VII; RR = CH_2) (1·0 g.) and phosphorus oxychloride (6·0 c.c.) were gently refluxed for 50 minutes. The oxychloride was removed under reduced pressure from the dark red solution, and the residual red gum was washed with light petroleum (b. p. 40—60°), taken up in methyl alcohol (3 c.c.), cooled to 0°, and basified by the gradual addition of methyl-alcoholic ammonia (5 c.c. of saturated solution). The mixture was poured into water (30 c.c.), extracted twice with methylene dichloride, dried (Na_2SO_4), and freed from solvent. The residual oil solidified on trituration with a little methyl alcohol, and the product crystallised from ethyl acetate in glistening orange-red elongated prisms (or needles) (0·5 g.), m. p. 204—205° (Found: C, 66·1; H, 5·0. $C_{21}H_{19}O_6N$ requires C, 66·2; H, 5·0%). This interesting highly-coloured *base* was decomposed by boiling it with dilute hydrochloric acid to give oxyhydrastinine, m. p. 98°, and meconine, m. p. 102°; this degradation confirmed its structure. It was sparingly soluble in cold dilute acids, methyl or ethyl alcohol, or benzene, but soluble in chloroform, yielding an orange-red solution. It did not appear to be reduced by zinc in dilute hydrochloric acid.

Hydrastine-a and Hydrastine-b.—Finely powdered dehydrohydrastine (VIII; RR = CH_2) (0·75 g.) was suspended in glacial acetic acid (60 c.c.) and shaken with platinic oxide (10 mg.) in an atmosphere of hydrogen for 2 hours. The colourless solution was filtered, the solvent removed under reduced pressure, and the residual gum basified with aqueous ammonia and extracted with methylene dichloride. After drying of the extract the solvent was removed, and the product was taken up in methyl alcohol (4 c.c.) and mixed with a solution of picric acid (0·42 g.) in methyl alcohol (3 c.c.). The mixture was warmed for a few minutes, and next morning the crude picrate (1·15 g.) was collected and refluxed with acetone (15 c.c.) for ½ hour. The residue (0·5 g.) separated from a large volume of methyl ethyl ketone in glistening yellow prisms, m. p. 217—218° (Found: C, 52·9; H, 4·1. Calc. for $C_{31}H_{29}O_{19}N_3$: C, 52·9; H, 3·9%), which gave no depression in m. p. when mixed with hydrastine-a picrate.

The acetone filtrate, on concentration to about 5 c.c. gave the *hydrastine-b picrate*, which separated from acetone in clusters of stout yellow prisms, m. p. 197—198° (Found: C, 52·9; H, 4·2%).

The picrates (0·25 g.) were decomposed with methyl-alcoholic ammonia; most of the methyl alcohol was then removed and the residue, after the addition of dilute aqueous ammonia, was extracted first with methylene dichloride (5 c.c.) and then with ether (10 c.c.). The combined extracts were washed several times with dilute ammonia solution and dried, the solvents removed, and the bases recovered quantitatively. Hydrastine-a crystallised from ether or methyl alcohol in glistening stout prisms, m. p. 138—139° (Found: C, 65·7; H, 5·5. Calc. for $C_{11}H_{11}O_4N$: C, 65·8; H, 5·5%).

Hydrastine-*b* separated from methyl alcohol in stout colourless prisms, m. p. 151—152° (Found: C, 65·5; H, 5·4%). The two bases showed no depression in m. p. when mixed with specimens of hydrastine-*a* or -*b* respectively.

Attempts to resolve Hydrastine-b.—*Hydrastine-b hydrogen (+)-tartrate* was prepared by warming equimolecular quantities of base and (+)-tartaric acid in water, extra tartaric acid being added in small quantities until dissolution was complete and until the unchanged base did not separate on cooling; it separated from water in clusters of felted needles, m. p. 60—70° (Hope, Pyman, Remfry, and Robinson, *J.*, 1931, 236, give m. p. 65—70°) (Found: C, 49·9; H, 5·6; H_2O, 13·1. Calc. for $C_{25}H_{27}O_{16}N,4H_2O$: C, 49·6; H, 5·8; H_2O, 13·3%), which after being dried *in vacuo* over phosphoric oxide melted at 115—120° and had $[\alpha]_D^{20}$ = +8·3° in water (*c*, 1·28). The (+)-*camphor-10-sulphonate*, prepared in alcoholic solution, separated in small colourless prisms, m. p. 183—186° (Found: C, 60·5; H, 6·0. $C_{31}H_{37}O_{10}NS$ requires C, 60·5; H, 6·0%), $[\alpha]_D^{17}$ = +7·5° in water (*c*, 0·86). The (−)-*camphor-10-sulphonate* separated from alcohol in slender, colourless prisms, m. p. 180—185° (Found: C, 60·1; H, 6·0%), $[\alpha]_D^{20}$ = −13·0° in water (*c*, 0·5). The (+)-*bromocamphor-10-sulphonate*, prepared in aqueous solution, separated from methyl alcohol in clusters of colourless elongated prisms, m. p. 225—230°, with slight previous softening (Found: C, 53·8; H, 5·4. $C_{31}H_{41}O_{19}NSBr$ requires C, 53·6; *d*, 5·2%), which had $[\alpha]_D^{20}$ = +42·0° in methyl alcohol (*c*, 0·4).

Resolution of (±)-Hydrastine-a.—(+)-Hydrastine-*a* hydrogen (+)-tartrate, prepared in alcoholic solution, crystallised from water in glistening silky needles, m. p. 110—111° (Hope, Pyman, Remfry, and Robinson, *loc. cit.*, give m. p. 108—110°), which had $[\alpha]_D^{20}$ = +6·6° in water (*c*, 0·4).

The (+)-camphor-10-sulphonate, prepared in aqueous solution, separated from water in glistening

white needles, m. p. 135—140°, with previous softening at 125° (Hope, Pyman, Remfry, and Robinson, *loc. cit.*, give m. p. 145° with sintering at 135°). Systematic fractional crystallisation of this *salt* (1·6 g.) from water yielded glistening colourless needles (0·6 g.), m. p. 120—122° after sintering at 110° (Found: C, 57·4; H, 6·3; H_2O, 5·4. $C_{21}H_{21}O_{10}NS,2H_2O$ requires C, 57·2; H, 6·3; H_2O, 5·5%), $[\alpha]_D^{15} = -25·4°$ in water (*c*, 1·3), unchanged by further crystallisation. The base (0·4 g.) liberated by addition of aqueous ammonia and isolated with methylene dichloride, had in the crude state $[\alpha]_D^{15} = +26·7°$ in chloroform (*c*, 0·2); crystallisation from methyl alcohol gave optically inactive (±)-hydrastine-*a* (0·2 g.), m. p. 138—139°, and (+)-*hydrastine*-*a* which separated from methyl alcohol in colourless prisms, m. p. 131—132° (Found: C, 65·8; H, 5·4. $C_{21}H_{21}O_6N$ requires C, 65·8; H, 5·5%), depressed to 127—128° when mixed with (±)-hydrastine-*a*. (+)-Hydrastine which had $[\alpha]_D^{15} = +42·2°$ in chloroform (*c*, 0·2) gave a *picrate* which separated from alcohol in glistening yellow needles, m. p. 185° (rapid heating, otherwise collapses at 155—160°) (Found: C, 52·3; H, 4·3; loss at 80°, 4·9%. $C_{27}H_{24}O_{13}N_4,CH_3{\cdot}OH$ requires C, 52·2; H, 4·3; $CH_3{\cdot}OH$, 5·0%).

Concentration of the (+)-camphor-10-sulphonate mother-liquors yielded a semi-solid mass which on basification gave a crude base (0·5 g.), $[\alpha]_D^{15} = -30·2°$ in chloroform (*c*, 0·25). After 2 crystallisations from methyl alcohol, (−)-hydrastine-*a* (0·4 g.) was obtained as glistening colourless prisms, m. p. 131—132° (Found: C, 66·1; H, 5·7%), depressed to 127—128° when mixed with (±)-hydrastine-*a*, but converted into (±)-hydrastine-*a*, m. p. 138—139°, by crystallisation from a methyl-alcoholic solution containing an equal weight of (+)-hydrastine-*a*, and giving no depression in m. p. when mixed with a specimen of naturally occurring (−)-hydrastine, m. p. 133°. (−)-Hydrastine-*a* had $[\alpha]_D^{15} = -42·1°$ in chloroform (*c*, 0·2) and under similar conditions naturally occurring (−)-hydrastine had $[\alpha]_D^{15} = -41·7°$. The *picrate* of synthetic (−)-hydrastine-*a* separated from alcohol in glistening yellow needles, m. p. 185° (rapid heating, otherwise collapses at 155—160°) (Found, in material dried at 80°: C, 53·2; H, 3·9. $C_{27}H_{24}O_{13}N_4$ requires C, 52·9; H, 3·9%), undepressed when mixed with the picrate prepared from natural (−)-hydrastine.

N-Methyl-N-(2-3′ : 4′-dimethoxyphenylethyl)meconine-a-carboxyamide (VII; R = Me), prepared as described for (VII; RR = CH_2), crystallised from methyl alcohol in glistening white prisms, m. p. 123—124° (Found: C, 63·7; H, 6·2. $C_{23}H_{25}O_7N$ requires C, 63·6; H, 6·0%).

Dehydrocordrastine (VIII; R = Me), prepared and isolated as described for dehydrohydrastine (VIII; RR = CH_2), was crystallised first from methyl alcohol and then from ethyl acetate; it formed orange-yellow prisms, m. p. 136—136·5° (Found: C, 66·2; H, 5·9. $C_{22}H_{23}O_6N$ requires C, 66·5; H, 5·8%).

Cordrastine I and Cordrastine II (I; R = Me).—Dehydrocordrastine (5 g.) was reduced in acetic acid (50 c.c.) as described in a similar case. Reduction was complete in 1 hour, and the product, isolated with methylene dichloride, was crystallised from methyl alcohol. *Cordrastine I* gradually separated in long, thin prisms (2·4 g.), m. p. 155—156° (Found: C, 66·4; H, 6·2. $C_{22}H_{25}O_6N$ requires C, 66·2; H, 6·3%). The *picrate* crystallised from methyl alcohol in stout yellow prisms, m. p. 153—154° (Found: loss in wt. at 90°, 1·4; C, 52·6; H, 4·5. $C_{28}H_{28}O_{13}N_4,\frac{1}{2}H_2O$ requires loss in wt., 1·4; C, 52·8; H, 4·6%).

The (+)-*camphor-10-sulphonate*, prepared in alcohol and precipitated by the careful addition of ether, crystallised from acetone in colourless, felted needles, m. p. 175—180° (Found: C, 61·2; H, 6·8. $C_{32}H_{41}O_{10}NS$ requires C, 60·9; H, 6·5%), $[\alpha]_D^{15} = +9·2°$ in water (*c*, 1·0). The (−)-*camphor-10-sulphonate*, prepared similarly, separated from acetone in felted needles, m. p. 175—180° (Found: loss in wt. at 100°, 1·4; C, 59·8; H, 6·6. $C_{32}H_{41}O_{10}NS,\frac{1}{2}H_2O$ requires loss in wt., 1·4; C, 60·0; H, 6·5%), $[\alpha]_D^{15} = -7·7°$ in water (*c*, 1·0). The (+)-*bromocamphor-10-sulphonate*, prepared from ammonium (+)-bromocamphor-10-sulphonate in aqueous solution, crystallised from methyl alcohol in elongated prisms, m. p. 215—218° (Found: C, 54·0; H, 5·6. $C_{32}H_{40}O_{10}NSBr$ requires C, 54·1; H, 5·6%), $[\alpha]_D^{15} = +34·8°$ in water (*c*, 1·1). The hydrogen (+)- and (−)-tartrates were uncrystallisable syrups.

A solution of picric acid (1·4 g.) in methyl alcohol (5 c.c.) was added to the hot methyl-alcoholic mother-liquors from which cordrastine-I had separated, and the picrate (3·3 g.) which separated on cooling was collected and refluxed with methyl alcohol (30 c.c.) for 30 minutes. The undissolved *cordrastine II picrate* (3·0 g.) was collected and crystallised from acetone in stout yellow rhombs, m. p. 202° (decomp.) with previous shrinkage at 165—170° (Found: C, 53·4; H, 4·6. $C_{34}H_{31}O_{19}N_4$ requires C, 53·5; H, 4·5%). Decomposition with methyl-alcoholic ammonia yielded *cordrastine II*, which crystallised from ether in colourless rhombic prisms, m. p. 118—119° (Found: C, 66·0; H, 6·3%). The *hydrogen* (−)-*tartrate*, prepared in alcohol, crystallised from methyl alcohol in clusters of slender colourless prism, m. p. 153—156° (Found: loss in wt. at 80°, 5·5; C, 56·0; H, 6·0. $C_{44}H_{51}O_{18}N,CH_3{\cdot}OH$ requires loss in wt., 5·5; C, 55·8; H, 6·0%). $[\alpha] = [\alpha]_D^{15} -7·4°$ in water (*c*, 1·0).

Our thanks are offered to Messrs. T. and H. Smith Ltd., Edinburgh, for generous gifts of narcotine and hydrastine, to Sir Robert Robinson for specimens of hydrastine-*a* and -*b*, and to the Department of Scientific and Industrial Research and Imperial Chemical Industries Limited, Dyestuffs Division, for Maintenance Grants to one of us (A. R. P.).

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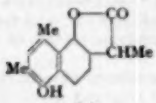
361. *The Constitution of ψ-Santonin. Part VII. Some Dimethylethylnaphthols.*

By Wesley Cocker, B. E. Cross, A. K. Fateen, Cyril Lipman, E. R. Stuart, W. H. Thompson, and D. R. A. Whyte.

Dehydrogenation of desmotropo-ψ-santonin with palladised charcoal yields a dimethylethylnaphthol. Spectroscopic studies suggest that it is 2 : 4-dimethyl-6-ethyl-1-naphthol (II). Several new dimethylethylnaphthols are described.

Clemo and Cocker (*J.*, 1946, **30**) showed that deoxy-ψ-santonin is dehydrogenated with selenium to 1-methyl-7-ethylnaphthalene and that desmotropo-ψ-santonin yields 2 : 4-dimethyl-1-naphthol on fusion with sodium hydroxide. On the basis of this evidence the structure (I) was assigned to desmotropo-ψ-santonin. We have now found conditions whereby desmotropo-ψ-santonin is dehydrogenated, with palladised charcoal (cf. Cocker *et al.*, *Chem. and Ind.*, 1949, 641) to a dimethylethylnaphthol.

This naphthol fails to couple with diazotised *p*-nitroaniline. It is thus substituted in the *ortho*- and *para*-positions to the phenolic group. Further, ultra-violet and infra-red light-absorption studies suggest that the new naphthol is 2 : 4-dimethyl-6-ethyl-1-naphthol (II), an expected dehydrogenation product of a desmotropo-compound of structure (I). The synthesis of (II) has not yet been accomplished, and further work on this is in progress.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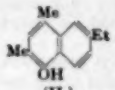
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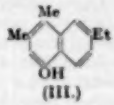
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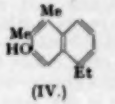
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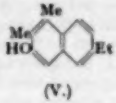
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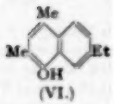
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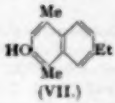
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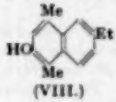
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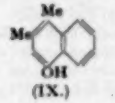
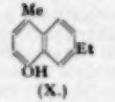

(IX.)


(X.)

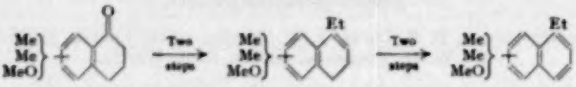
Only one dimethylethylnaphthol has so far been described, namely, 1 : 4-dimethyl-6-ethyl-3-naphthol obtained by the fusion of an artemisic or dihydroartemisic acid with potassium hydroxide (Bertolo, *Gazzetta*, 1926, **56**, 856). It is now shown that this naphthol is also obtained when (−)-α-desmotroposantonin is heated at 240—250° with palladised charcoal, and the identity of the naphthol has been confirmed by synthesis.

We had access to four xylenols, namely *o*-3-, *o*-4-, *m*-4-, and *p*-xylenol, from which we have prepared a number of naphthols possessing an ethyl group in the non-phenolic ring, namely, 3 : 4-dimethyl-6-ethyl-1-naphthol (III), 1 : 2-dimethyl-5- (IV) and -6-ethyl-3-naphthol (V), 2 : 4-dimethyl-7-ethyl-1-naphthol (VI), 1 : 4-dimethyl-6-ethyl-3- (VII) and -2-naphthol (VIII). In addition, 3 : 4-dimethyl-1-naphthol (IX) (cf. Arnold, Buckley, and Richter, *J. Amer. Chem. Soc.*, 1947, **69**, 2323; Kruber and Schade, *Ber.*, 1935, **68**, 11) and 4-methyl-7-ethyl-1-naphthol (X) have been prepared. 3 : 4-Dimethyl-1-naphthol (IX) was obtained by the condensation of succinic anhydride with *o*-4-xylyl methyl ether and *via* the following compounds: β-(2-methoxy-4 : 5-dimethylbenzoyl)propionic acid, γ-(2-methoxy-4 : 5-dimethylphenyl)butyric acid, 1-keto-5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene, and 5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene.

Naphthols substituted by Ethyl in an α-Position in the Non-phenolic Nucleus.—The method followed (cf. Haworth, *J.*, 1932, 1125, 2717; Haworth, Letsky, and Mavin, *ibid.*, p. 1784) involved the reaction of ethylmagnesium iodide with the appropriate tetralone followed by dehydration of the product and dehydrogenation of the unsaturated compound so formed.

The three tetralones employed, namely, 1-keto-5-methoxy-7 : 8-dimethyl-, 1-keto-8-methoxy-5 : 7-dimethyl- (Cocker and Lipman, *J.*, 1947, **53**; Cocker, Lipman, and Whyte, preceding paper), and 1-keto-7-methoxy-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Cocker, *J.*, 1946, **36**), condensed readily with the Grignard reagent and the corresponding dihydro-

naphthalene derivatives were obtained in good yield. These were satisfactorily demethylated with hydriodic acid, but in two cases subsequent attempts to effect dehydrogenation gave



anomalous results. Thus, 4-methoxy-1 : 2-dimethyl-8-ethyl-5 : 6-dihydronaphthalene, obtained from the first-mentioned tetralone, yielded 3 : 4-dimethyl-1-naphthol (IX); and 5-methoxy-6 : 8-dimethyl-4-ethyl-1 : 2-dihydronaphthalene obtained from the second-mentioned tetralone, gave 2 : 4-dimethyl-1-naphthol when heated with selenium at 340° or sulphur at 210°. On the other hand, 1 : 2-dimethyl-5-ethyl-3-naphthol (IV) was directly produced when 3-methoxy-1 : 2-dimethyl-5-ethyl-7 : 8-dihydronaphthalene, obtained from the last of the three tetralones mentioned, was heated with hydriodic acid containing free iodine. However, this reagent did not give satisfactory results with the other dihydro-compounds. Neither chloranil nor *N*-bromosuccinimide was successful as dehydrogenating agent. Catalytic reduction of the dihydro-compounds followed by dehydrogenation also led to the loss of the ethyl group and the production of much tarry material.

Unsatisfactory results were also obtained when 5-hydroxy-7 : 8-dimethyl-4-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene [obtained from ethyl β-(2-methoxy-4 : 5-dimethylbenzoyl)propionate through the stages 4-(2-methoxy-4 : 5-dimethylphenyl)hex-3-enoic acid •, 4-(2-methoxy-4 : 5-dimethyl)phenylhexanoic acid, and 1-keto-5-hydroxy-7 : 8-dimethyl-4-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene] or its methyl ether was submitted to dehydrogenation. None of the required 1 : 2-dimethyl-5-ethyl-1-naphthol was obtained.

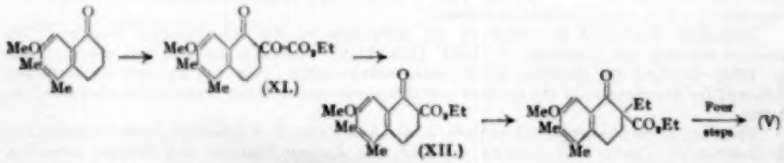
It is significant that, in our experience, loss of alkyl group was experienced only in those compounds where this group was present in an α-position in the reduced ring and where there was another group in the corresponding α-position of the aromatic ring. We propose to investigate this point more fully.

Other workers have met similar dealkylation during dehydrogenation (cf. Ramage, *J.*, 1938, 1853) but amongst the examples of the phenomenon, which we have found in the literature, that mentioned by Ruzicka, Ehmann, and Morgeli (*Helv. Chim. Acta*, 1933, **16**, 314, 325) approaches most closely to those described by us. These workers found that 2 : 7-dimethyl-1-ethyl-3 : 4-dihydronaphthalene is partly converted into 2 : 7-dimethylnaphthalene when heated with selenium at 300°.

When 4-methoxy-1 : 2-dimethyl-8-ethyl-5 : 6-dihydronaphthalene was catalytically reduced and the product was heated with palladised charcoal at 300°, 1 : 2-dimethyl-8-ethylnaphthalene was obtained and characterised as its picrate and its trinitrobenzene and trinitrotoluene adducts. A similar result was obtained when the hydroxy-compounds were dehydrogenated. Ruzicka, Hofmann, and Frei (*Helv. Chim. Acta*, 1936, **19**, 386) recorded that 3-methoxy-2 : 6-dimethylnaphthalene is converted into 2 : 6-dimethylnaphthalene when heated with palladised charcoal. Further investigation of this point is in hand.

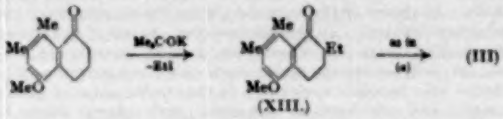
Naphthols substituted by Ethyl in a β-Position in the Non-phenolic Nucleus.—Numerous methods are available for the synthesis of alkylnaphthalenes in which the alkyl group is in a β-position, and many are applicable to the synthesis of the corresponding naphthols. Some of these are illustrated schematically below, using actual examples employed in the present investigation.

(*a*) (cf. Cocker and Lipman, *J.*, 1947, 523):

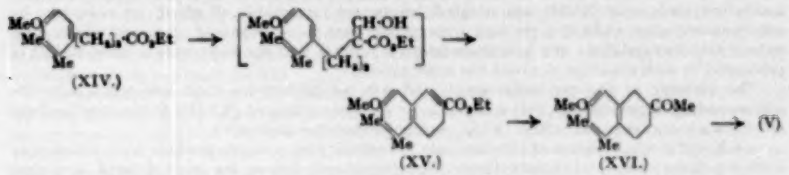


• Geneva nomenclature.

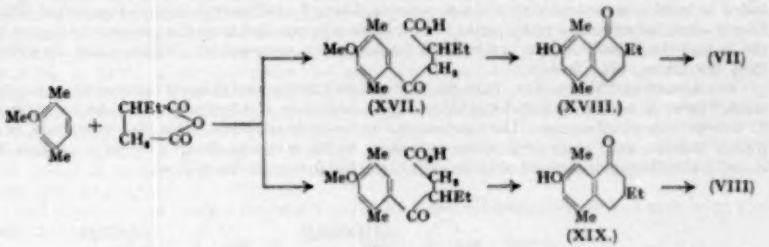
(*b*) (cf. Koebner and Robinson, *J.*, 1941, 573) :



(*c*) (cf. Holmes and Trevoy, *Org. Synth.*, 1946, **26**, 28) :



(*d*) (cf. Haworth, *J.*, 1932, 1128) :



Method (a). By this route ethyl 1-keto-7-methoxy-5 : 6- (XI) and 1-keto-5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-glyoxylate and the corresponding carboxylates were obtained, but only the carboxylate (XII) derived from (XI) was successfully ethylated.

Method (b). 1-Keto-7-methoxy-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Cocker, *loc. cit.*) was directly ethylated using potassium *tert.*-butoxide, but apparently *gem*-diethyl compounds were produced, since subsequent Clemmensen reduction was very slow and the reduction product resisted dehydrogenation (as shown by ultra-violet light absorption measurements). This agrees with the experience of Clemo and Dickenson (*J.*, 1937, 255) who showed that 2 : 2-dimethyl- and 2-methyl-2-ethyltetralin resisted the action of selenium. Sen Gupta (*J. pr. Chem.*, 1938, [ii], **151**, 82) asserted that the former yields 2-methylnaphthalene when heated with selenium in a sealed tube but, in our case, this modification also failed.

1-Keto-5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene, however, was directly ethylated to 1-keto-5-methoxy-7 : 8-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (XIII) which was converted in the usual way into 3 : 4-dimethyl-6-ethyl-1-naphthol (III).

Method (c). From the appropriate butyric esters, ethyl 7-methoxy-5 : 6- (XV) and 8-methoxy-5 : 7-dimethyl-3 : 4-dihydronaphthalene-2-carboxylate were obtained although the yields left much to be desired. These were reduced to the tetrahydro-compounds, hydrolysed, and converted into the acid chlorides, which were not isolated but were treated immediately with dimethylcadmium. No reaction took place, presumably owing to insolubility of the reaction mixture in the solvent but, by the action of methylmagnesium iodide on 7-methoxy-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxyamide a very small quantity of a ketone, probably 7-methoxy-2-acetyl-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (XVI), was obtained.

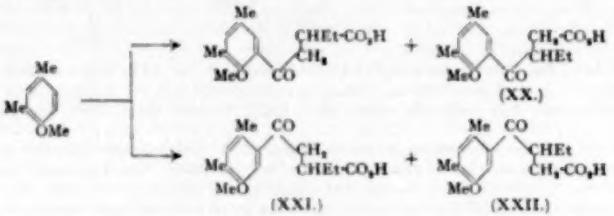
Method (d). This provides a very direct route to the required naphthols. The first stage consists in the condensation of ethylsuccinic anhydride with the appropriate xylyl ether. The

subsequent stages are well known. Using methylsuccinic anhydride, the method has been extensively applied to the synthesis of polycyclic hydrocarbons (cf. Berliner, *Org. Reactions*, **1949**, **5**, 242, 275). As shown in the formulæ above, the reaction may yield either an α- or a β-alkyl-δ-benzoylpropionic acid. In general, however, the use of an ionising solvent favours the formation of the α-alkyl compound, whereas non-ionising solvents act in the reverse sense (cf. Cocker *et al.*, *loc. cit.*, who review the earlier work on the condensation of unsymmetrical alkylsuccinic anhydrides with aromatic systems). In the condensation of methylsuccinic anhydride (unpublished work) and ethylsuccinic anhydride with phenyl ethers in nitrobenzene, the α-alkyl-β-benzoylpropionic acids generally predominate. With *p*-xylyl methyl ether, however, ethylsuccinic anhydride yields a mixture from which pure β-(4-methoxy-2 : 5-dimethylbenzoyl)-α-ethylpropionic acid (XVII) was isolated, leaving an intractable oil which, on reduction by amalgamated zinc, yielded a product from which pure β-(4-methoxy-2 : 5-dimethylbenzyl)-*n*-valeric acid was isolated; the quantities isolated indicate that the anhydride condensation had proceeded in each direction to about the same extent.

The identity of the two acids mentioned was established by their conversion into the corresponding tetralones (XVIII) and (XIX). The keto-group of (XVIII) is hindered and did not form a semicarbazone, whilst (XIX) readily yielded this derivative.

o-4-Xylyl methyl ether and ethylsuccinic anhydride give a sticky product from which only α-ethyl-β-(2-methoxy-4 : 5-dimethylbenzoyl)propionic acid has so far been isolated in a pure condition. This compound, after reduction to the corresponding butyric acid, was readily cyclised to 1-keto-5-methoxy-7 : 8-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene, which failed to yield a semicarbazone but was converted into 3 : 4-dimethyl-6-ethyl-1-naphthol (III). In our view, failure of a 1-tetralone to yield a semicarbazone indicates the presence of groups in the 2- and the 8-position and can be used for diagnostic purposes (cf. Cagniant and Buu-Hoï, *Bull. Soc. chim.*, **1942**, **9**, 841).

Von Auwers and Mauss (*Ber.*, **1928**, **61**, 1495) showed that acetyl chloride reacts with *m*-4-xylyl methyl ether in boiling carbon disulphide to yield a mixture of 5-hydroxy-2 : 4- and 2-hydroxy-3 : 5-dimethylacetophenone. The reaction of ethylsuccinic anhydride with the ether could, in a similar fashion, take place both *ortho*- and *meta*- to the methoxy-group to yield a mixture of α- and β-ethylbenzoylpropionic acids in each case, that is four products in all:



When we condensed ethylsuccinic anhydride with *m*-4-xylyl methyl ether in cold nitrobenzene, a mixture was obtained in which α-ethyl-β-(5-methoxy-2 : 4-dimethylbenzoyl)-propionic acid (XXI) predominated. Its identity was established by oxidation to 5-methoxy-2 : 4-dimethylbenzoic acid [obtained from the known 5-methoxy-2 : 4-dimethylacetophenone (von Auwers and Mauss, *loc. cit.*)], and by reduction followed by cyclisation to 1-keto-8-hydroxy-5 : 7-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. From this ketone, which failed to give a semicarbazone or a piperonylidene derivative, 8-hydroxy-5 : 7-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (*A*) and thence 2 : 4-dimethyl-7-ethyl-1-naphthol (VI) were obtained.

In addition to the keto-acid already mentioned, we obtained an appreciable quantity of an intractable, oily keto-acid. This yielded a tetralone from which a pure semicarbazone was eventually obtained. The semicarbazone was reduced by the Huang-Minlon modification of the Wolff–Kishner reaction to the foregoing tetralin (*A*), which also gave the naphthol (VI); assuming that no isomeric changes took place during the reduction, it must be concluded that the semicarbazone was derived from 1-keto-5-methoxy-6 : 8-dimethyl-3-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene which must have originated from β-ethyl-β-(2-methoxy-3 : 5-dimethylbenzoyl)propionic acid (XX). Oxidation of the oily keto-acid yielded an impure sample of

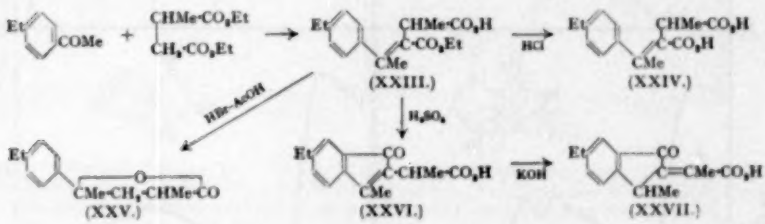
5-methoxy-2 : 4-dimethylbenzoic acid and, thus, it is obvious that the oil also contains (XXI) or the unknown (XXII), or both.

It is of interest that, when we condensed chloroacetyl chloride with *m*-4-xylyl methyl ether in cold nitrobenzene, ω-chloro-5-methoxy-2 : 4-dimethylacetophenone was the sole product isolated. Its identity was established by reduction to 5-methoxy-2 : 4-dimethylacetophenone. In cold carbon disulphide, the same product was isolated in good yield but there was evidence of other products (cf. von Auwers and Mauss, *loc. cit.*).

Amongst other products prepared from *m*-4-xylyl methyl ether was 5-methoxy-2 : 4-dimethylbenzyl alcohol which was obtained in excellent yield by the reduction of 5-methoxy-2 : 4-dimethylbenzoic acid with lithium aluminium hydride in ether. The derived benzyl chloride with ethyl ethylmalonate gave ethyl 5-methoxy-2 : 4-dimethylbenzylethylmalonate, hydrolysed to an oily acid, which was further reduced with lithium aluminium hydride to an alcohol, but attempts to convert the last into the corresponding chloride were not successful. We intend to investigate these reactions further.

The syntheses so far described started with the appropriate xylenol to which a second ring carrying an ethyl group was fused. Attempts were made, starting with ethylbenzene, to fuse on the phenolic nucleus. The first method we employed in this connection was that due to Stobbe (cf. Campbell, *Annual Reports*, 1947, **44**, 136, for many references). Methylsuccinic ester was condensed with *p*-ethylacetophenone to yield a mixture of unsaturated acids from which 3-carbethoxy-4-*p*-ethylphenyl-2-methylpent-3-enoic acid (XXIII) was isolated. Attempted decarboxylation of this half ester with concentrated hydrochloric acid yielded only the corresponding dicarboxylic acid (XXIV or an isomer), m. p. 142°; but in hydrobromic acid in acetic acid the half-ester yielded the lactone of 4-hydroxy-4-*p*-ethylphenyl-2-methylpentanoic acid (XXV). Distillation of the half-ester under reduced pressure yielded a second dicarboxylic acid (m. p. 155°), which on storage was gradually transformed into the lower-melting acid. The relationship of these acids has still to be investigated. Attempted cyclisation of the half-ester with concentrated sulphuric acid yielded a colourless keto-compound, m. p. 83°, which when refluxed with alcoholic potash gave an isomeric yellow compound, m. p. 122°. The former compound is probably α-(1-keto-3-methyl-6-ethyl-2-indenyl)propionic acid (XXVI) (cf. Campbell, *loc. cit.*) and the latter the more highly conjugated α-(1-keto-3-methyl-6-ethyl-2-indanylidene)propionic acid (XXVII).

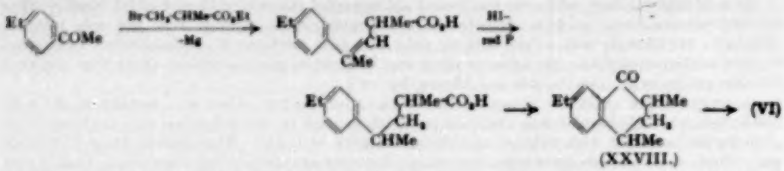
All attempts to obtain the required 2 : 4-dimethyl-7-ethyl-1-naphthol or its 3-carboxylic acid were unsuccessful.



The following method was then employed. *p*-Ethylacetophenone was condensed, in boiling xylene, with ethyl β-bromo*iso*butyrate in presence of magnesium. The magnesium dissolved fairly rapidly under these conditions and the product was hydrolysed, yielding an oil, probably a mixture of the required 4-*p*-ethylphenyl-2-methylpent-3-enoic acids. Attempted ring-closure of this oil with phosphorus trichloride (cf. Borsche, *Annalen*, 1936, **526**, 1) yielded the lactone (XXV), and treatment of the lactone with concentrated sulphuric acid gave a product which possessed the odour of a naphthol but proved intractable.

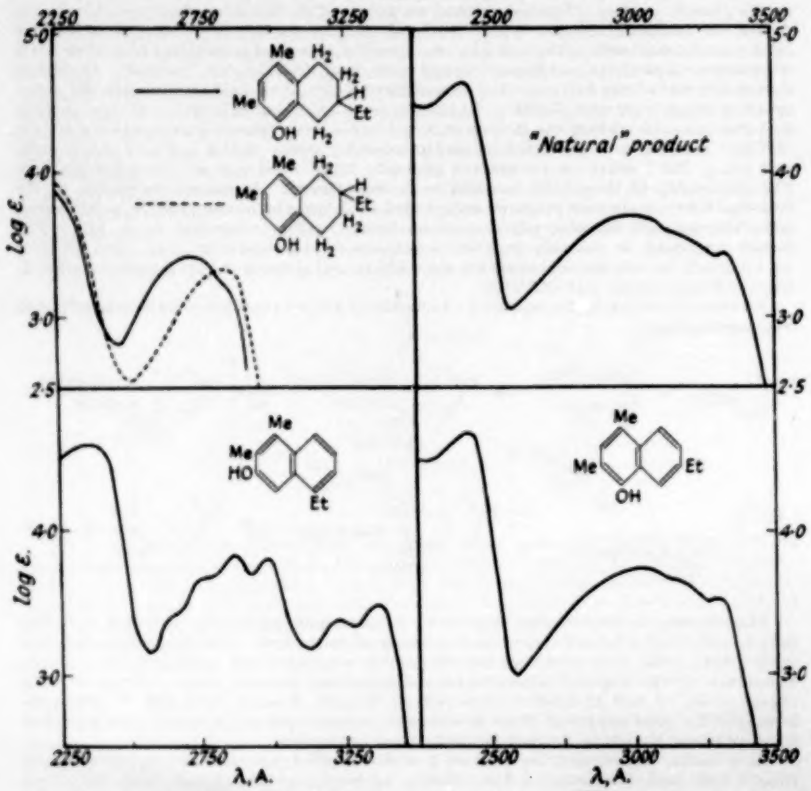
In a further experiment, designed as a model, methyl β-*p*-ethylbenzoylpropionate was treated with methylmagnesium iodide yielding 4-*p*-ethylphenylpent-3-enoic acid, but efforts to cyclise this to 4-methyl-7-ethyl-1-naphthol with phosphorus trichloride (Borsche, *loc. cit.*), acetic anhydride, or sulphuric acid gave either the acid chloride or intractable material. The acid chloride could not be cyclised and it would appear that, in spite of the work of Borsche, these unsaturated acids are not suitable for cyclisation to phenolic

compounds (cf. also Fieser and Fieser, "Natural Products Related to Phenanthrene," New York, 1949, p. 87).



However, when the mixture of 4-(*p*-ethylphenyl)-2-methylpent-3-enoic acids was reduced with hydriodic acid and red phosphorus, a product was obtained which was cyclised in sulphuric acid to 1-keto-2 : 4-dimethyl-7-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (XXVIII). Bromin-

FIG. 1.



ation in ether and dehydrobromination with dimethylaniline yielded the required 2 : 4-dimethyl-7-ethyl-1-naphthol (VI) which did not depress the melting point of the compound prepared by the route already described.

By a similar process, 4-*p*-ethylphenylpent-3-enoic acid gave 1-keto-4-methyl-7-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene and thence 4-methyl-7-ethyl-1-naphthol (X).

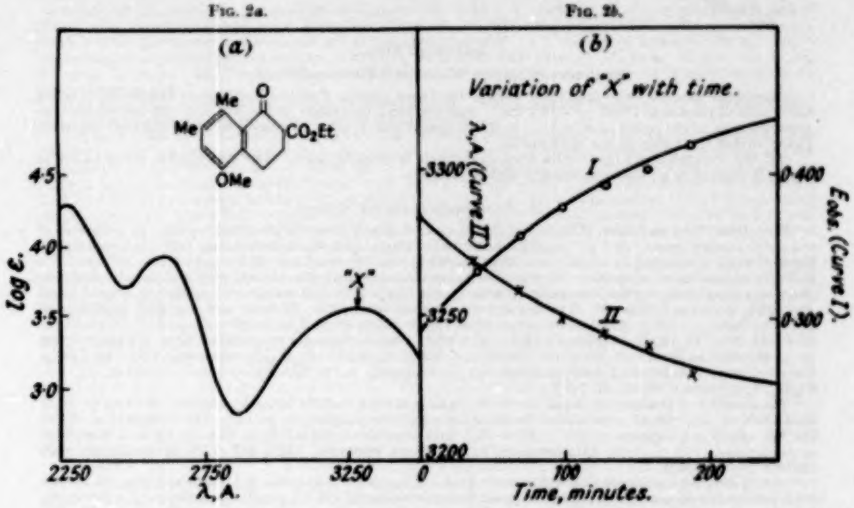
Few examples of the use of β-bromo-esters in the Reformatsky reaction are to be found in the literature. In the case in point, the reaction did not proceed in presence of zinc under any conditions employed. Magnesium reacted slowly in boiling benzene, but very rapidly in boiling xylene, and the yields of the product were of the order of 45%. Bromination of the tetralone followed by dehydrobromination was very smooth and this method appears to us to be of considerable preparative value.

Absorption Spectra.—The absorption spectra of the various naphthols and some related compounds were measured (see Experimental section) and Fig. 1 shows typical examples.

The 1- may be clearly distinguished from the 2-naphthols, particularly by the " triplet " and " doublet " bands of the latter, and here the degree of resolution in the " triplets " and " doublets " varies with the position of the substituent alkyl groups.

The carbethoxy-tetralones showed an interesting phenomenon. One of the peaks (denoted by X in Fig. 2*a*) alters with time in respect to position and also intensity. Measurement of this

Fig. 2a. Fig. 2b.



change is illustrated in Fig. 2*b*. However, there was no simultaneous change in the peak at 2290 A. and only a slight fall in $E_{obs.}$ for the peak at 2610 A. Further studies of this problem are in hand, but the phenomenon is likely to be associated with the equilibrium shown below :

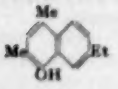
Fig. 1 shows conclusively that the " natural " naphthol from desmotropo-ϕ-santonin is a 1-naphthol. Furthermore, its ultra-violet light absorption shows such a close resemblance to that of 2 : 4-dimethyl-7-ethyl-1-naphthol that it probably differs from the latter only in the possession of a 6- in place of a 7-ethyl group.

The infra-red absorption spectra of 4-methyl- and 2 : 4-dimethyl-7-ethyl-1-naphthol and the " natural " naphthol have been examined (see table) by Messrs. Imperial Chemical Industries Limited, Billingham Division, who report that the " natural " naphthol and 2 : 4-dimethyl-7-ethyl-1-naphthol have spectra of the same clear, well-defined type, but that there are many

differences in detail which are consistent with a shift in the position of the ethyl group from the 7- to the 6-position, but that they are inconsistent with a shift to the 5- or the 8-position.

Infra-Red Absorption.

The numerals give the band frequencies (cm.$^{-1}$), the letters the band strength (W = weak, M = medium, S = strong).

"Natural" naphthol	773 W	826 S	880 S	931 M	987 W	1030 W	1049 W	1108 M	1162 M	1193 W	1225 W	1244 W	1276 W	1309 M
	815 S	847 M	870 M	889 M	940 W	1002 W	1033 W	1055 W	1071 W	1101 M	1162 M	1195 M	1238 M	1306 M	1337 W
	825 S	888 M	918 W	1035 W	1051 S	1144 M	1162 W	1196 M	1220 W	1253 W	1274 W				

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Absorption spectra were measured with a Beckman Quartz Spectrophotometer, Model D.U., using silica cells of thickness 1·000 ± 0·001 cm. Spectra were measured in alcohol and the initial concentrations were of the order of 20 mg./l., with ten-fold dilution when necessary to bring the high intensity peaks within the range of the instrument.

All the Friedel–Crafts reactions were performed in nitrobenzene. The description given under *A* below is typical of all the experiments in this category.

A. Experiments with o-4-*Xylenol.*

3 : 4-*Dimethyl*-1-*naphthol* (IX).—*β*-(2-*Methoxy*-4 : 5-*dimethylbenzoyl*)*propionic acid*. A mixture of *o*-4-xylyl methyl ether (26·8 g.), succinic anhydride (22 g.), and dry nitrobenzene (100 c.c.) was slowly treated with a solution of aluminium chloride (25 g.) in nitrobenzene (200 c.c.) at 15—20°, and the mixture was set aside overnight. It was then poured into ice and hydrochloric acid, and the nitrobenzene layer was separated, washed successively with hydrochloric acid and water, and extracted several times with 20% aqueous ammonia. The extract was washed with ether, filtered, and acidified, yielding the *keto-acid* (26·5 g.; m. p. 155°), which crystallised from dilute alcohol as needles, m. p. 161° (Found: C, 66·1; H, 7·1. $C_{15}H_{18}O_4$ requires C, 66·1; H, 6·8%). Its *methyl* ester crystallised from light petroleum (b. p. 40—60°) as stout rods, m. p. 58° (Found: C, 66·8; H, 7·15. $C_{16}H_{20}O_4$ requires C, 67·2; H, 7·2%). Its *ethyl* ester consisted of needles (from light petroleum), m. p. 73—74° (Found: C, 67·9; H, 7·9. $C_{17}H_{22}O_4$ requires C, 68·2; H, 7·6%).

The identity of the keto-acid was shown by oxidation with sodium hypochlorite to 2-*methoxy*-4 : 5-*dimethylbenzoic acid*, which crystallised from dilute alcohol as needles, m. p. 141—142° (Found: C, 66·8; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%), and was also obtained from 2-methoxy-4 : 5-dimethylacetophenone (von Auwers, Bundesmann, and Wieners, *Annalen*, 1926, **447**, 176) by oxidation with sodium hypochlorite.

γ-(2-*Methoxy*-4 : 5-*dimethylphenyl*)*butyric acid*.—The keto-acid (14·4 g.), refluxed for 24 hours with amalgamated zinc (50 g.), concentrated hydrochloric acid (50 c.c.) and water (30 c.c.), yielded the *butyric acid* (12·6 g.) which crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 78—79° (Found: C, 69·9; H, 8·1. $C_{15}H_{22}O_3$ requires C, 70·3; H, 8·1%).

1-*Keto*-5-*methoxy*-7 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. The butyric acid (12·5 g.) was heated for 10 minutes at 65—70° with concentrated sulphuric acid (60 c.c.), cooled, and poured on crushed ice, and the *ketone* was collected (11·6 g.). It was washed successively with sodium carbonate and water and crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 76° (Found: C, 76·5; H, 8·0. $C_{15}H_{18}O_2$ requires C, 76·5; H, 7·8%). Its *semicarbazone* crystallised from dilute alcohol as silvery plates, m. p. 205—206° (Found: C, 63·7; H, 7·0. $C_{16}H_{21}O_2N_3$ requires C, 64·4; H, 7·3%).

5-*Hydroxy*-1-*keto*-7 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* was obtained when the butyric acid was heated with 80% sulphuric acid on the water-bath for 2 hours. It crystallised from dilute alcohol as prisms, m. p. 193—194° (Found: C, 75·6; H, 7·3. $C_{14}H_{16}O_2$ requires C, 75·8; H, 7·4%).

5-*Methoxy*-7 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. 1-Keto-5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (17·2 g.) was reduced during 24 hours with a mixture of concentrated hydrochloric acid (140 c.c.), water (100 c.c.), and amalgamated zinc (140 g.), and the product was extracted with ether. The required *methoxytetralin* was obtained as a colourless oil (9·3 g.), b. p. 152°/6 mm. (Found: C, 81·6; H, 9·2. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

5-*Hydroxy*-7 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. The last-mentioned methoxy-compound (9·0 g.) was refluxed for 90 minutes with hydriodic acid (*d* 1·7; 45 c.c.). The *product* (4·7 g.) crystallised from light petroleum (b. p. 60—80°) as felted needles, m. p. 116—117° (Found: C, 81·6; H, 8·7. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%). Its *carbanilate* crystallised from dilute alcohol as prisms, m. p. 145—146° (Found: C, 76·8; H, 7·0. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·1%).

3 : 4-*Dimethyl*-1-*naphthol* (IX). The preceding compound (1 g.) was heated with selenium (3 g.) for

2·25 hours at 330—340° and the product was extracted with benzene (charcoal) and distilled in steam. The distillate yielded the naphthol (0·2 g.) which crystallised from light petroleum (b. p. 60—80°) as prisms, m. p. 121·5° (Arnold, Buckley, and Richter, *loc. cit.*, give m. p. 121—122°, and Kruber and Schade, *loc. cit.*, give m. p. 114—115°) (Found : C, 83·4; H, 7·0. Calc. for $C_{15}H_{12}O$: C, 83·7; H, 7·0%). Light absorption : Maxima, 2420, 3060 (3160), and 3300 A.; log ε = 4·43, 3·89 (3·85), and 3·73, respectively. Its *picrate* crystallised from benzene as scarlet needles, m. p. 168° (Found : C, 53·9, 53·7; H, 4·0, 3·9. $C_{15}H_{12}O_8N_3$ requires C, 53·9; H, 3·7%). Its 3 : 5-*dinitrobenzoate* crystallised from benzene–light petroleum as needles, m. p. 222—224° (Found : C, 61·6; H, 2·9. $C_{19}H_{14}O_6N_2$ requires C, 62·3; H, 3·8%).

3 : 4-*Dimethyl*-6-*ethyl*-1-*naphthol* (III).—*Ethyl* 1-*keto*-5-*methoxy*-7 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*glyoxylate*. 1-Keto-5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (30·6 g.) in freshly distilled ethyl oxalate (21·3 g.) and absolute alcohol (150 c.c.) was cooled to −5° and a solution of sodium (3·45 g.) in alcohol (60 c.c.) was added at −5°. Next morning the solution was poured into a mixture of ice and concentrated hydrochloric acid. The *glyoxylate* which separated crystallised from alcohol as golden needles (25 g.), m. p. 90—91° (Found : C, 67·1; H, 6·5. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

Ethyl 1-*keto*-5-*methoxy*-7 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylate*. The preceding compound (21·5 g.) was heated with powdered glass (30 g.) at 190—200° until evolution of carbon monoxide ceased. The product was collected (b. p. 200—208°/10 mm.) and crystallised from light petroleum (b. p. 40—60°) as silky needles (12·5 g.), m. p. 62·5—63·5° (Found : C, 70·1; H, 6·9. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·2%).

α-*Ethyl*-β-(2-*methoxy*-4 : 5-*dimethylbenzoyl*)*propionic acid*. A mixture of *o*-4-xylyl methyl ether (22 g.), ethylsuccinic anhydride (cf. Wren and Crawford, *J.*, 1937, 230) (22 g.), and nitrobenzene (30 c.c.), treated with aluminium chloride (50 g.) in nitrobenzene (100 c.c.), yielded a *keto-acid* (21 g.) which crystallised from dilute alcohol as tufts of needles, m. p. 138—142° (Found : C, 68·4; H, 7·7. $C_{18}H_{26}O_4$ requires C, 68·2; H, 7·6%). Its identity was confirmed by oxidation to 2-methoxy-4 : 5-dimethylbenzoic acid.

γ-(2-*Methoxy*-4 : 5-*dimethylphenyl*)-α-*ethylbutyric acid*. The foregoing keto-acid (21 g.) was reduced under Clemmensen conditions to an oil which failed to solidify.

1-*Keto*-5-*methoxy*-7 : 8-*dimethyl*-2-*ethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIII) was obtained (3·6 g.) as an oil, b. p. 168°/10 mm., when the above oil (5 g.) was heated with concentrated sulphuric acid (25 c.c.) for 10 minutes at 65—70° (Found : C, 77·6; H, 8·7. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%). It failed to yield a semicarbazone. This compound was also obtained when 1-keto-5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (5 g.), dissolved in a stirred solution of potassium (16 g.) in *tert.*-butyl alcohol (382 c.c.), was slowly treated with ethyl iodide (100 c.c.), and the mixture refluxed for 2 hours. Removal of solvent and addition of water yielded an oil (5·3 g.) which was extracted with ether, washed with sulphurous acid, dried, and distilled (Found : C, 77·7; H, 8·5%).

5-*Hydroxy*-7 : 8-*dimethyl*-2-*ethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. The foregoing oily ketone (9 g.) was reduced under Clemmensen conditions and the product was refluxed for 2·5 hours with hydriodic acid (25 c.c.) and glacial acetic acid (10 c.c.). The *hydroxy*-compound, which was extracted with ether, crystallised from light petroleum (b. p. 40—60°) as lustrous needles (6 g.), m. p. 97—98° (Found : C, 82·3; H, 10·1. $C_{14}H_{20}O$ requires C, 82·4; H, 9·8%). Light absorption : Maxima, 2200 A., log ε = 3·96; 2850 A., log ε = 3·32. This compound (Found : C, 82·2; H, 9·8%) was also obtained from the 1-keto-5-methoxy-7 : 8-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene obtained by direct ethylation.

3 : 4-*Dimethyl*-6-*ethyl*-1-*naphthol* (III). The preceding compound (0·8 g.) was dehydrogenated with selenium (2·4 g.) at 340—360° for 2·5 hours. The *product* (0·48 g.) crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 76—77° (Found : C, 84·4; H, 8·0. $C_{14}H_{14}O$ requires C, 84·0; H, 8·0%). Its *picrate* crystallised from benzene–light petroleum (b. p. 40—60°) as scarlet needles, m. p. 135—136° (Found : C, 55·3; H, 4·4. $C_{20}H_{17}O_8N_3$ requires C, 55·9; H, 4·4%). Light absorption : Maxima, 2450 (2920) and 3050 (3100) A.; log ε = 4·67 (3·64) and 3·64 (3·71) respectively.

Attempts to prepare 3 : 4-*Dimethyl*-5-*ethyl*-1-*naphthol*.—4-*Methoxy*-1 : 2-*dimethyl*-8-*ethyl*-5 : 6-*dihydronaphthalene*. 1-Keto-5-methoxy-7 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (5·3 g.) in dry ether (75 c.c.) was slowly added to a solution of ethylmagnesium iodide, from ethyl iodide (10 c.c.) in ether (75 c.c.). The reaction was completed by 1 hour's refluxing and the mixture was decomposed with ice and hydrochloric acid and extracted with ether from which the unsaturated *compound* was obtained as an oil (4·9 g.), b. p. 156—159°/8 mm. (Found : C, 82·7; H, 9·0. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%).

When this product (6 g.) was refluxed with hydriodic acid (16 c.c.) for 2 hours and the product heated with selenium (8 g.) at 330—340° for 3·5 hours, the mixture yielded much tarry material and 3 : 4-dimethyl-1-naphthol (0·5 g.), m. p. 121·5°. A similar result was obtained when the product of the Grignard reaction was directly heated with selenium and then demethylated with hydrogen iodide.

1 : 2-*Dimethyl*-8-*ethylnaphthalene* (Found : C, 91·4; H, 8·6. $C_{14}H_{16}$ requires C, 91·3; H, 8·7%) was obtained (0·45 g.) as a colourless oil, b. p. 145—146°/10 mm., when the above unsaturated compound (0·6 g.) was reduced in acetic acid with palladised charcoal and the product was heated with palladised charcoal (0·5 g.) for 2 hours at 300—320°. Light absorption : Maxima, 2280, 2610, 2880, and 3210 A.; log ε = 4·72, 3·59, 3·69, and 2·81, respectively. Its *picrate* crystallised from methyl alcohol as orange-red needles, m. p. 91° (Found : C, 59·0; H, 4·35. $C_{20}H_{19}O_7N_3$ requires C, 58·1; H, 4·6%). Its *trinitrobenzene* derivative crystallised from methanol as dark yellow needles, m. p. 109° (Found : C, 60·5; H, 4·5. $C_{26}H_{19}O_6N_3$ requires C, 60·45; H, 4·8%). Its *trinitrotoluene* derivative crystallised from methanol as dark yellow needles, m. p. 82° (Found : C, 61·1; H, 4·9. $C_{21}H_{21}O_6N_3$ requires C, 61·3; H, 5·2%).

2-*Hydroxy*-4 : 5-*dimethylstyryl ethyl ketone*. 2-Hydroxy-4 : 5-dimethylbenzaldehyde (2·55 g.), prepared by the modification of the Gattermann reaction described by Adams and Levine (*J. Amer. Chem. Soc.*, 1923, **45**, 2373; Adams and Montgomery, *ibid.*, 1924, **46**, 1518), in 10% sodium hydroxide (35 c.c.) was treated with methyl ethyl ketone (10 c.c.) in water (80 c.c.). The solution was then refluxed for 3 days, acidified, and extracted with ether, from which the *ketone* was obtained as a brown oil. It quickly solidified and was thrice recrystallised from benzene–light petroleum (b. p. 60—80°) and obtained (0·5 g.)

as pale yellow needles, m. p. 143° (Found: C, 76·3; H, 7·9. $C_{13}H_{14}O_3$ requires C, 76·5; H, 7·8%). It yielded a 2:4-dinitrophenylhydrazone, m. p. 239—240°.

Attempts to obtain 1:2-*Dimethyl*-5-*ethyl*-4-*naphthol*.—4-(2-*Methoxy*-4:5-*dimethylphenyl*)*hex*-3-*enoic acid*. Ethyl β-(2-methoxy-4:5-dimethylbenzoyl)propionate (18 g.) in ether (250 c.c.) was added at 0° to a Grignard solution from ethyl iodide (15 g.). After being stirred for 2 hours in the cold the mixture was refluxed for 1 hour and decomposed with ammonium chloride. The ethereal layer was separated and extracted 3 times with 10% sodium carbonate, from which an oily mixture of isomeric acids (9·5 g.) was obtained. On rubbing with light petroleum (b. p. 40—60°) one of the required *acids* solidified and was crystallised from light petroleum as tablets, m. p. 82·5° (Found: C, 72·3; H, 8·2. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

4-(2-*Methoxy*-4:5-*dimethylphenyl*)*hexanoic acid*. Hydrogenation of either the mixture of acids or the pure acid mentioned above in presence of platinic oxide in ethyl acetate gave a quantitative yield of the saturated *acid*. It crystallised from light petroleum as sheaves of needles, m. p. 82—83°, depressed to 70° by its precursor (Found: C, 72·1; H, 9·5. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%).

The *lactone* of 4-hydroxy-4-(2-methoxy-4:5-dimethylphenyl)hexanoic acid was obtained when the above unsaturated acid was heated with potassium hydrogen sulphate at 160°. It crystallised from ligroin as prisms, m. p. 98—99° (Found: C, 72·7; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

5-*Hydroxy*-1-*keto*-7:8-*dimethyl*-4-*ethyl*-1:2:3:4-*tetrahydronaphthalene*. The hexanoic acid (7 g.), heated with 80% sulphuric acid (40 c.c.) at 100° for 3·5 hours, gave a mixture of the required *hydroxyketone* (2·5 g.), which crystallised from ligroin as fine needles, m. p. 156—157° (Found: C, 76·6; H, 8·4. $C_{15}H_{18}O_3$ requires C, 77·1; H, 8·2%), and its *methyl ether*, b. p. 160—163°/10 mm. (Found: C, 77·9; H, 9·3. $C_{16}H_{20}O_3$ requires C, 77·6; H, 8·6%).

5-*Hydroxy*-7:8-*dimethyl*-4-*ethyl*-1:2:3:4-*tetrahydronaphthalene and its methyl ether*. The preceding compounds were reduced under Clemmensen conditions, yielding the required *hydroxytetralins* as colourless oils, b. p. 158—160°/10 mm. (Found: C, 82·3; H, 10·1. $C_{14}H_{20}O$ requires C, 82·3; H, 9·8%) and 140—142°/10 mm. (Found: C, 82·5; H, 10·3. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%), respectively. Efforts to dehydrogenate these compounds were unsuccessful.

B. Experiments with o-3-*Xylenol.*

1:2-*Dimethyl*-5-*ethyl*-3-*naphthol* (IV).—3-*Methoxy*-1:2-*dimethyl*-5-*ethyl*-7:8-*dihydronaphthalene*. 1-Keto-7-methoxy-5:6-dimethyl-1:2:3:4-tetrahydronaphthalene (Cocker, *J.*, 1946, 36) (5·7 g.), allowed to react in the usual way with ethylmagnesium iodide [prepared from ethyl iodide (9·2 c.c.)], yielded an oil (6·1 g.) which was heated at 160° with potassium hydrogen sulphate (6·0 g.). The mixture was extracted with ether, yielding the required *ether* (2·8 g.), which crystallised from methanol as prisms, m. p. 82·5° (Found: C, 84·0; H, 8·5. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%).

1:2-*Dimethyl*-5-*ethyl*-3-*naphthol* (IV). The foregoing dihydro-compound (0·7 g.) was simultaneously demethylated and dehydrogenated when refluxed for 2 hours with hydriodic acid containing iodine (4 c.c.). The product was first sublimed and was then crystallised from light petroleum (b. p. 60—80°), yielding the *naphthol* as feathery needles (0·5 g.), m. p. 121° (Found: C, 83·5, 83·8; H, 7·9, 8·0. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). Light absorption: Maxima, 2380, 2760, 2860, 2970, 3230, and 3370 A.; log ε = 4·62, 3·68, 3·85, 3·82, 3·39, and 3·49, respectively. Its *picrate* crystallised from benzene–light petroleum (b. p. 80—100°) as deep-red needles, m. p. 118—119° (Found: C, 55·5; H, 4·4. $C_{20}H_{19}O_8N_3$ requires C, 55·9; H, 4·4%).

1:2-*Dimethyl*-6-*ethyl*-3-*naphthol* (V).—*Ethyl* γ-(4-*methoxy*-2:3-*dimethylphenyl*)*butyrate* was obtained as an oil, b. p. 166—168°/2—3 mm., when the corresponding acid (Cocker, *J.*, 1946, 36) was refluxed for 4 hours with alcohol and sulphuric acid (Found: C, 72·1; H, 8·8. $C_{16}H_{24}O_3$ requires C, 72·0; H, 8·8%).

Ethyl 7-*methoxy*-5:6-*dimethyl*-3:4-*dihydronaphthalene*-2-*carboxylate*. Absolute alcohol (8 c.c.) was slowly added to powdered sodium (3·14 g.) in dry ether (65 c.c.), and the mixture was refluxed until the sodium had dissolved. The solution was cooled to −15° and a mixture of the above ester (15·7 g.), ethyl formate (9·5 c.c.), and ether (50 c.c.) was added dropwise with stirring during 1 hour. The mixture was set aside at room temperature for 72 hours, powdered ice was added, and the ethereal layer containing unchanged butyric ester (8·5 g.) was separated. The aqueous layer was acidified and the crude formyl compound (3·8 g.) which separated was collected with ether and dried. The solvent was removed and the residue was added at −10° to a well-stirred mixture of 90% phosphoric acid (15·5 c.c.) and concentrated sulphuric acid (3·3 c.c.). The mixture, allowed to warm to 10° during 2 hours, was poured on ice and extracted with ether. The aqueous solution was nearly neutralised with sodium hydroxide and again extracted with ether. The combined extracts, washed first with sodium hydrogen carbonate and then with water and dried, yielded the required *ester* (3·35 g.) which crystallised from dilute alcohol as needles, m. p. 65—68° (Found: C, 73·7; H, 7·8. $C_{15}H_{20}O_3$ requires C, 73·8; H, 7·7%). Light absorption: Maxima, 2440, 3020, and 3350 A.; log ε = 4·25, 4·13, and 3·88, respectively.

7-*Methoxy*-5:6-*dimethyl*-3:4-*dihydronaphthalene*-2-*carboxylic acid* separated from alcohol as prisms, m. p. 232° (Found: C, 72·0; H, 7·1. $C_{13}H_{16}O_3$ requires C, 72·4; H, 6·9%). Light absorption: Maxima, 2430, 3020, and 3330 A.; log ε = 4·25, 4·1, and 3·84, respectively.

7-*Methoxy*-5:6-*dimethyl*-1:2:3:4-*tetrahydronaphthalene*-2-*carboxylic acid* was obtained (1·3 g.) when the preceding compound (1·35 g.) was reduced in ethyl acetate (100 c.c.) using palladised charcoal (0·1 g.). The saturated acid crystallised from dilute alcohol as prisms, m. p. 190° (Found: C, 71·8; H, 7·65. $C_{13}H_{18}O_3$ requires C, 71·8; H, 7·7%). Its *amide*, prepared from the crude acid chloride, crystallised from dilute alcohol as needles, m. p. 216° (Found: C, 71·9; H, 7·8. $C_{13}H_{19}O_2N$ requires C, 72·1; H, 8·2%).

7-*Methoxy*-2-*acetyl*-5:6-*dimethyl*-1:2:3:4-*tetrahydronaphthalene*. A suspension of the above amide (0·5 g.) in anisole (50 c.c.) was added to a Grignard solution prepared from magnesium (0·7 g.) and ethyl iodide (4·2 g.) in anisole (25 c.c.), and the mixture was refluxed in an atmosphere of nitrogen for 80 hours. The mixture was worked up in the usual way and the product (50 mg.) was crystallised from alcohol, from

which the required *ketone* separated as clusters of needles, m. p. 120—122° (Found: C, 76·8; H, 8·3. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%). It yielded a 2 : 4-dinitrophenylhydrazone.

Ethyl 1-keto-7-methoxy-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-glyoxylate (XI). 1-Keto-7-methoxy-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Cocker, *loc. cit.*) (10 g.) was condensed in the usual way with ethyl oxalate in presence of potassium ethoxide. The *glyoxylate* (7·5 g.; m. p. 94—95°) crystallised from alcohol as scarlet prisms, m. p. 95—96° (Found: C, 66·7; H, 6·7. $C_{17}H_{20}O_4$ requires C, 67·1; H, 6·6%). Light absorption: Maxima, 3250 A.; log ε = 4·01; 3750 A.; log ε = 4·02.

Ethyl 1-keto-7-methoxy-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylate (XII) was obtained (1·8 g.) when the glyoxylate (2 g.) was heated for 1 hour with powdered glass (3 g.). It crystallised from alcohol as needles, m. p. 99·5° (Found: C, 69·1; H, 7·7. $C_{17}H_{22}O_4$ requires C, 69·6; H, 7·2%). Light absorption: Maxima, 2240, 2710, 3100, and 3290 A.; log ε = 4·26, 4·1, 3·63, and 3·70, respectively.

1-Keto-7-methoxy-5 : 6-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. A solution of the preceding compound (3·7 g.) in *tert.*-butyl alcohol (40 c.c.) was added to potassium *tert.*-butoxide [from potassium (2·0 g.) and *tert.*-butyl alcohol (60 c.c.)]. Ethyl iodide (15 c.c.) was then slowly added, with stirring, in the cold, and the mixture was refluxed for 3 hours and set aside overnight. The alcohol was removed, the residue was diluted with water and extracted with ether and the extract was washed several times with cold 40% sodium hydroxide solution. The dried extract was distilled, yielding an oil (1·7 g.), b. p. 174—180°/5 mm., which was refluxed for 2 hours with potassium hydroxide (0·5 g.) in methyl alcohol (10 c.c.). The solid product was crystallised several times from light petroleum (b. p. 40—60°), from which the required *ketone* separated as prisms (0·5 g.), m. p. 66° (Found: C, 77·4; H, 8·5. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%).

7-Hydroxy-5 : 6-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. The preceding compound (0·4 g.) was reduced under Clemmensen conditions and gave an oil which was refluxed for 1·5 hours with hydriodic acid (4 c.c.) and acetic acid (10 c.c.). The required *hydroxytetralin* (0·3 g.) crystallised from light petroleum (b. p. 60—80°) as prisms, m. p. 93° (Found: C, 82·0; H, 9·5. $C_{14}H_{20}O$ requires C, 82·4; H, 9·8%). Light absorption: Maxima, 2200 A., log ε = 3·94; 2870 A., log ε = 3·41.

α-Ethyl-β-(4-methoxy-2 : 3-dimethylbenzoyl)propionic acid. o-3-Xylyl methyl ether (16 g.) was condensed with ethylsuccinic anhydride (16 g.) and aluminium chloride (26 g.). The product was crystallised several times from benzene–light petroleum (b. p. 100—120°), from which the required *acid* (18 g.) separated as needles, m. p. 135° (Found: C, 67·7; H, 7·5. $C_{18}H_{24}O_4$ requires C, 68·2; H, 7·6%).

α-Ethyl-γ-(4-methoxy-2 : 3-dimethylphenyl)butyric acid. The above keto-acid (12·2 g.), reduced under Clemmensen conditions, yielded a solid which, after 3 crystallisations from light petroleum (b. p. 40—60°), yielded the required *acid* (12·2 g.) as radiating needles, m. p. 78° (Found: C, 71·7; H, 8·7. $C_{17}H_{26}O_3$ requires C, 72·0; H, 8·8%). Heated for 10 minutes at 65—70° with concentrated sulphuric acid (10 c.c.), this (2·7 g.) yielded 1-keto-7-methoxy-5 : 6-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (2·0 g.), m. p. 66°, undepressed by the ketone prepared as described above. It yielded 7-hydroxy-5 : 6-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene after reduction and demethylation.

1 : 2-Dimethyl-6-ethyl-3-naphthol (V). 7-Hydroxy-5 : 6-dimethyl-2-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (0·4 g.) was heated with powdered selenium (1·2 g.) for 2·5 hours at 340—360°. The product was crystallised from benzene–light petroleum (b. p. 40—60°) from which the required *naphthol* (0·15 g.) separated as long needles, m. p. 102—102·5° (Found: C, 84·4; H, 8·2. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). Light absorption: Maxima, 2370 (2740), 2860 (2960), 3190, and 3330 A.; log ε = 4·81 (3·55), 3·64 (3·54), 3·22, and 3·34, respectively.

Direct Ethylation of 1-Keto-7-methoxy-5 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene.—This ketone (3 g.) was added to a solution of potassium (9·6 g.) in *tert.*-butyl alcohol (180 c.c.), and the mixture stirred for 1 hour with ethyl iodide (60 c.c.) and then refluxed for 2 hours. The product, an oil (2·9 g.), b. p. 185°/5 mm., solidified and was then crystallised from light petroleum (b. p. 40—60°) from which it separated as prisms, m. p. 52—53° (Found: C, 78·0, 78·6; H, 8·8, 9·2. $C_{17}H_{24}O_2$ requires C, 78·5; H, 9·2%). The product was probably *1-keto-7-methoxy-5 : 6-dimethyl-2 : 2-diethyl-1 : 2 : 3 : 4-tetrahydronaphthalene*. Complete reduction of this ketone (3 g.) under Clemmensen conditions took about 72 hours, the supposed *7-methoxy-5 : 6-dimethyl-2 : 2-diethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* being obtained as an oil (1·7 g.), b. p. 166°/1—2 mm. (Found: C, 82·2; H, 10·5. $C_{17}H_{26}O$ requires C, 82·9; H, 10·6%).

When the ketone (1 g.) was heated for 1 hour with hydriodic acid (5 c.c.) it yielded a glass which solidified on being rubbed with light petroleum (b. p. 40—60°). On crystallisation from this solvent the supposed *7-hydroxy-1-keto-5 : 6-dimethyl-2 : 2-diethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* separated as needles, m. p. 149° (Found: C, 77·7; H, 8·6. $C_{16}H_{24}O_2$ requires C, 78·0; H, 8·9%).

C. Experiments with m-4-*Xylenol.*

Attempts to prepare 1 : 3-Dimethyl-5-ethyl-4-naphthol.—1-Keto-8-methoxy-5 : 7-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (5 g.) (cf. Cocker and Lipman, and Cocker, Lipman, and Whyte, *loc. cit.*) and ethylmagnesium iodide [from ethyl iodide (4 c.c.)] gave *5-methoxy-6 : 8-dimethyl-4-ethyl-1 : 2-dihydronaphthalene* as an oil (2·9 g.), b. p. 135°/10 mm. (Found: C, 82·9; H, 9·1. $C_{16}H_{22}O$ requires C, 83·3; H, 9·2%). When this compound (3·4 g.) was heated with sulphur (1·2 g.) at 205—210° for 4 hours and the product demethylated, 2 : 4-dimethyl-1-naphthol was produced.

Ethyl γ-(5-methoxy-2 : 4-dimethylphenyl)butyrate, prepared from the corresponding acid (Cocker and Lipman, *loc. cit.*), distilled at 157°/3 mm. (Found: C, 72·0; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%).

Ethyl 5-methoxy-6 : 8-dimethyl-1 : 2-dihydronaphthalene-3-carboxylate was obtained (2·3 g.) as a yellow oil from the above ester (10 g.) by condensation with ethyl formate (see above). It was refluxed for 4 hours with 10% methyl-alcoholic potash (40 c.c.), yielding *5-methoxy-6 : 8-dimethyl-1 : 2-dihydronaphthalene-3-carboxylic acid* (1·9 g.), which separated from dilute alcohol in needles, m. p. 212—213° (Found: C, 71·7, 72·0; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

5-Methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-3-carboxylic Acid.—The preceding compound was quantitatively reduced in ethyl acetate over palladised charcoal, yielding the required saturated *acid* which separated from alcohol as prisms, m. p. 158° (Found: C, 71·9; H, 7·45. $C_{14}H_{18}O_3$

requires C, 71·8; H, 7·7%). Its *amide* separated from dilute alcohol as needles, m. p. 199—200° (Found: C, 71·8; H, 8·3. $C_{18}H_{19}O_3N$ requires C, 72·1; H, 8·2%).

2:4-*Dimethyl*-7-*ethyl*-1-*naphthol* (VI).—*α-Ethyl-β-(5-methoxy*-2:4-*dimethylbenzoyl)propionic acid* (XXI). *m*-4-Xylyl methyl ether (31 g.) condensed with ethylsuccinic anhydride (30 g.) and aluminium chloride (25 g.) to yield a sticky product which solidified when rubbed with benzene–light petroleum (b. p. 60—80°). After several crystallisations from this mixture the required *acid* was obtained as colourless needles (11 g.), m. p. 64°•(Found: C, 68·1; H, 7·65. $C_{18}H_{26}O_4$ requires C, 68·2; H, 7·6%). Its *semicarbazone* separated from alcohol as needles, m. p. 165—166° (Found: C, 59·6; H, 7·0. $C_{19}H_{29}O_4N_3$ requires C, 59·8; H, 7·2%). Oxidation of the keto-acid with sodium hypochlorite yielded *5-methoxy*-2:4-*dimethylbenzoic acid* which separated from dilute alcohol as needles, m. p. 164° (Found: C, 66·7; H, 6·6. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). It was demethylated with hydriodic acid in acetic acid to 5-hydroxy-2:4-dimethylbenzoic acid, which crystallised from dilute alcohol as plates, m. p. 185—186° (Meisenheimer, Hanssen, and Wachterowitz, *J. pr. Chem.*, 1928, [ii], **119**, 315, give m. p. 185—186°). 5-Methoxy-2:4-dimethylbenzoic acid was also obtained by the oxidation of the known 5-methoxy-2:4-dimethylacetophenone (von Auwers and Mauss, *loc. cit.*) with sodium hypochlorite.

α-Ethyl-β-(5-hydroxy-2:4-*dimethylbenzoyl)propionic acid* obtained by heating the methoxy-acid with hydriodic acid separated from ethyl acetate–light petroleum as needles, m. p. 144° (Found: C, 67·0; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

8-Hydroxy-1-*keto*-5:7-*dimethyl*-2-*ethyl*-1:2:3:4-*tetrahydronaphthalene*.—The methoxy-acid (XXI) (7·5 g.) was reduced under Clemmensen conditions to an oil (7 g.) which was heated with 80% sulphuric acid (40 c.c.) for 2 hours on the water-bath and afforded *8-hydroxy*-1-*keto*-5:7-*dimethyl*-2-*ethyl*-1:2:3:4-*tetrahydronaphthalene* (4 g.), b. p. 163°/10 mm., which solidified and then crystallised from dilute alcohol as needles, m. p. 28° (Found: C, 76·9; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%).

8-Hydroxy-5:7-*dimethyl*-2-*ethyl*-1:2:3:4-*tetrahydronaphthalene*.—The preceding compound (3·5 g.) was reduced (Clemmensen); the *product* (3 g.) separated from light petroleum (b. p. 40—60°) as needles, m. p. 80° (Found: C, 82·8; H, 10·5. $C_{14}H_{22}O$ requires C, 82·4; H, 9·8%). Light absorption: Maxima, 2200 A., log ε = 4·05; 2720 A., log ε = 3·42.

2:4-*Dimethyl*-7-*ethyl*-1-*naphthol* (VI).—The foregoing hydroxytetralin (0·5 g.) was heated at 340—360° for 2·5 hours with selenium (1·5 g.), and the product was crystallised from light petroleum (b. p. 40—60°) from which the *naphthol* separated as needles m. p. 110° (Found: C, 83·3, 83·5; H, 8·1, 7·8. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). Light absorption: Maxima, 2400, 3030 (3160), and 3400 A.; log ε = 4·62, 3·72 (3·64), and 3·50, respectively. Its *carbanilate* separated from aqueous alcohol as needles, m. p. 144° (Found: C, 79·2; H, 6·5. $C_{21}H_{21}O_2N$ requires C, 79·0; H, 6·6%). Its *picrate* separated from benzene as scarlet needles, m. p. 123—124° (Found: C, 55·4; H, 4·6. $C_{20}H_{19}O_8N_3$ requires C, 55·9; H, 4·4%).

The mother-liquors from the crystallisation of the methoxy-keto-acid described yielded an oily acid. This (5 g.) was reduced (Clemmensen) and cyclised with concentrated sulphuric acid to a mixture of methoxytetralones (3·6 g.), b. p. 168°/3 mm. (Found: C, 77·4; H, 8·4. Calc. for $C_{13}H_{16}O_2$: C, 77·6; H, 8·6%), which yielded a *semicarbazone* (1·2 g.), m. p. 190—191° (Found: C, 65·7; H, 8·2. $C_{14}H_{19}O_2N_3$ requires C, 66·4; H, 8·0%). This was probably the semicarbazone of 1-*keto*-5-*methoxy*-6:8-*dimethyl*-3-*ethyl*-1:2:3:4-*tetrahydronaphthalene* since on reduction by the Huang-Minlon modification of the Wolff–Kishner reaction and then demethylation it (1·2 g.) afforded 8-hydroxy-5:7-dimethyl-2-ethyl-1:2:3:4-tetrahydronaphthalene (0·5 g.).

3-*Carbethoxy*-4-(*p-ethylphenyl*)-2-*methylpent*-3-*enoic Acid* (XXIII).—A mixture of *p*-ethylacetophenone (10·4 g.), ethyl methylsuccinate (21·2 g.), and *tert.*-butyl alcohol (15 c.c.) was added to a solution of potassium (1·32 g.) in *tert.*-butyl alcohol (60 c.c.), and the mixture was refluxed for 40 minutes. After cooling, the mixture was rendered faintly acid and the solvent was removed under reduced pressure. The residue was extracted with ether which was washed with water and then shaken several times with saturated sodium carbonate. The filtered alkaline extracts were acidified, yielding a mixture of half-esters as an orange oil (20 g.) which partly solidified. The solid half-*ester* (2 g.) was collected and crystallised from light petroleum (b. p. 40—60°) from which it separated as needles, m. p. 112—113° (Found: C, 70·0; H, 7·4. $C_{17}H_{22}O_4$ requires C, 70·4; H, 7·6%). The half-ester was refluxed with 15% hydrochloric acid, yielding 3-*carboxy*-4-(*p-ethylphenyl*)-2-*methylpent*-3-*enoic acid* which separated from water as needles, m. p. 142° (Found: C, 68·3; H, 6·9. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). On distillation, the oily half-ester yielded a *dicarboxylic acid*, m. p. 155° (Found: C, 68·2; H, 6·9%). On storage, the latter dicarboxylic acid was transformed into the former, m. p. 142°.

Lactone of 4-*Hydroxy*-4-(*p-ethylphenyl*)-2-*methylpentanoic acid* (XXV).—The oily half-ester (5 g.) was refluxed for several hours with a mixture of glacial acetic acid (15 c.c.) and 48% hydrobromic acid (20 c.c.), and the oily *lactone* (2·5 g.) was collected, having b. p. 182—184°/10 mm. (Found: C, 76·9; H, 8·2. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%).

α-(1-Keto-3-*methyl*-6-*ethyl*-2-*indenyl)propionic Acid* (XXVI).—The oily half-ester (1 g.) was heated at 65—70° for 10 minutes with concentrated sulphuric acid (5 g.). The *product* (0·3 g.) crystallised from benzene–light petroleum (b. p. 60—80°) as white needles, m. p. 83° (Found: C, 73·7; H, 6·6. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%). Its *semicarbazone* separated from benzene–light petroleum as needles, m. p. 190° (Found: C, 63·7; H, 6·3. $C_{16}H_{19}O_3N_3$ requires C, 63·8; H, 6·3%). *α-(1-Keto*-3-*methyl*-6-*ethyl*-2-*indanylidene)propionic acid* (XXVII) was obtained as yellow needles (from alcohol), m. p. 122°, when its isomer was heated with alcoholic potash (Found: C, 73·1; H, 6·1%).

1-*Keto*-2:4-*dimethyl*-7-*ethyl*-1:2:3:4-*tetrahydronaphthalene* (XXVIII).—A mixture of methyl β-bromoisobutyrate (58 g.) (Pickard and Lochte, *J. Amer. Chem. Soc.*, 1927, **49**, 15), *p*-ethylacetophenone (47·2 g.), and xylene (50 c.c.) was added to a boiling mixture of magnesium (8·4 g.) and xylene (50 c.c.) to which a crystal of iodine had been added. After 3 hours' refluxing and stirring, all the magnesium had dissolved; the mixture was then treated with dilute sulphuric acid and ice, and the dried xylene layer was distilled, yielding a viscous yellow oil (46·5 g.). This was refluxed for 2 hours with potassium

• Another modification of this acid melted at 83°. Crystallisation of the latter from dilute alcohol gave the form of m. p. 64°. Both gave the same benzoic acid on oxidation and on demethylation.

hydrogen sulphate (90 g.), and the unsaturated esters (34·6 g.) were collected at 170—220°/10 mm. Hydrolysis with alcoholic potash gave a liquid mixture of acids which when shaken with 70% sulphuric acid yielded the lactone of 4-hydroxy-4-(*p*-ethylphenyl)-2-methylpentanoic acid (Found: C, 77·4; H, 8·4%).

The mixture of unsaturated acids (3·0 g.) was refluxed with hydriodic acid (15 c.c.) and red phosphorus (3 g.) for 5 hours, yielding an oil which no longer decolorised bromine. The oil was heated on the water-bath for 1 hour with a mixture of concentrated sulphuric acid (7 c.c.) and water (1·5 c.c.), and 1-*keto*-2 : 4-*dimethyl*-7-*ethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XXVIII) was obtained as an oil (1·0 g.), b. p. 136°/10 mm. (Found: C, 83·2; H, 8·9. $C_{14}H_{18}O$ requires C, 83·2; H, 8·9%). Its *semicarbazone* separated as silvery plates (from dilute alcohol), m. p. 202—203° (Found: C, 68·9; H, 7·95. $C_{15}H_{21}ON_3$ requires C, 69·5; H, 8·1%).

2 : 4-*Dimethyl*-7-*ethyl*-1-*naphthol* (VI).—The ketone (XXVIII) (0·6 g.) in anhydrous ether (8 c.c.) was slowly treated at room temperature with bromine (0·15 c.c.) in ether (5 c.c.). After 15 minutes, the solution was washed with aqueous sodium hydrogen carbonate, and a colourless oil was obtained. This was refluxed with dimethylaniline (2·5 c.c.) for 30 minutes and the solution was then added to excess of dilute sulphuric acid and distilled in steam. The filtered distillate yielded the required naphthol which crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 110—111°, which gave no depression with the naphthol already described (Found: C, 83·7; H, 7·95%). Its picrate and carbanilate (Found: C, 78·7; H, 6·6%) gave no depression in m. p. with the compounds prepared by the alternative method described above.

ω-Chloro-5-*methoxy*-2 : 4-*dimethylacetophenone*.—A solution of aluminium chloride (42 g.) in nitrobenzene (100 c.c.) was added to a stirred mixture of *m*-4-xylyl methyl ether (29·5 g.) and chloroacetyl chloride (25 g.), and the solution was set aside overnight. It was treated in the usual way and the product was extracted with chloroform and distilled. The oil (22 g.) which collected at 160—170°/2—3 mm. solidified (m. p. 82—84°) and crystallised from benzene–light petroleum as plates, m. p. 85—86° (Found: C, 61·8; H, 6·0. $C_{11}H_{13}O_2Cl$ requires C, 62·1; H, 6·1%).

5-*Methoxy*-2 : 4-*dimethylbenzyl Alcohol*.—5-Methoxy-2 : 4-dimethylbenzoic acid (2·5 g.) in dry ether (175 c.c.) was added slowly to a stirred suspension of lithium aluminium hydride (1 g.) in dry ether (200 c.c.) at such a rate as to maintain gentle reflux. The mixture was then gently refluxed for a further 30 minutes, cooled, and slowly treated with water and then with dilute sulphuric acid, and the ethereal layer separated. It was washed several times with dilute sodium carbonate solution and dried and the solvent removed, yielding the required *alcohol* (2·35 g.) which separated from light petroleum (b. p. 40—60°) as needles, m. p. 56—57° (Found: C, 71·8; H, 8·9. $C_{11}H_{16}O_2$ requires C, 72·5; H, 8·4%).

5-*Methoxy*-2 : 4-*dimethylbenzyl Chloride*.—The above alcohol (10·7 g.) was slowly treated in the cold with thionyl chloride (7·7 g.). A further, equal quantity of thionyl chloride was then added and the mixture set aside overnight, whereafter it was gently refluxed for 30 minutes. Excess of thionyl chloride was removed, and the residue was washed with aqueous sodium carbonate, dried in ether, and distilled, yielding the *chloro*-compound as an oil (8·5 g.), b. p. 122°/3 mm. (Found: C, 64·9; H, 6·5. $C_{11}H_{15}OCl$ requires C, 65·0; H, 7·1%).

Ethyl (5-*Methoxy*-2 : 4-*dimethylbenzyl*)*ethylmalonate*.—A mixture of sodium ethoxide [from sodium (1·74 g.) and absolute alcohol (45 c.c.)], ethyl ethylmalonate (14·3 g.), and sodium iodide (1 g.) was slowly treated with the above chloride (8·5 g.). Stirring was continued for 30 minutes and the mixture was refluxed for 6 hours. It was processed in the usual way and the required *ester* was obtained as an oil (13 g.), b. p. 182°/1 mm. (Found: C, 68·5; H, 8·3. $C_{19}H_{28}O_4$ requires C, 67·9; H, 8·3%).

D. *Experiments with* p-*Xylenol.*

1 : 4-*Dimethyl*-6-*ethyl*-3-*naphthol* (VII).—α-*Ethyl*-β-(4-*methoxy*-2 : 5-*dimethylbenzoyl*)*propionic acid* (XVII). *p*-Xylyl methyl ether (9 g.) was condensed with ethylsuccinic anhydride (8·7 g.), by use of aluminium chloride (22·5 g.). The crude product (13·5 g.; m. p. 96—104°) was crystallised several times from ligroin (b. p. 120°), from which the required *acid* was obtained as radiating rods (4·05 g.), m. p. 123—124° (Found: C, 68·0; H, 7·4. $C_{18}H_{26}O_4$ requires C, 68·2; H, 7·6%). Its *semicarbazone* crystallised from methanol as needles, m. p. 184° (decomp.) (Found: C, 59·7; H, 7·2. $C_{19}H_{29}O_4N_3$ requires C, 59·8; H, 7·2%). The mother-liquors from the crystallisation of the acid yielded a solid, m. p. 97—107° (see below).

α-*Ethyl*-γ-(4-*methoxy*-2 : 5-*dimethylphenyl*)*butyric acid*. The keto-acid (XVII) (3·9 g.) was reduced by amalgamated zinc (40 g.) to the required *butyric acid*, which crystallised from light petroleum (b. p. 40—60°) as colourless rods (3·3 g.), m. p. 55—56° (Found: C, 71·9; H, 9·1. $C_{18}H_{28}O_3$ requires C, 72·0; H, 8·8%).

7-*Hydroxy*-1-*keto*-5 : 8-*dimethyl*-2-*ethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XVIII). The preceding compound (3·2 g.), heated with 80% sulphuric acid (15·5 c.c.) at 100° for 2 hours, yielded the *ketone* which crystallised from light petroleum (b. p. 40—60°) as radiating plates (1·45 g.), m. p. 78—79° (Found: C, 77·3; H, 8·6. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%). It did not yield a semicarbazone.

7-*Hydroxy*-5 : 8-*dimethyl*-2-*ethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. The foregoing ketone (1·1 g.) was reduced with amalgamated zinc, and the required *hydroxytetralin* was crystallised from light petroleum (b. p. 40—60°), from which it was deposited as prisms (0·66 g.), m. p. 75° (Found: C, 82·2; H, 9·6. $C_{14}H_{20}O$ requires C, 82·35; H, 9·8%).

1 : 4-*Dimethyl*-6-*ethyl*-3-*naphthol* (VII). The hydroxytetralin (0·45 g.) was dehydrogenated with selenium (1·5 g.) at 340—350° for 2 hours. The required naphthol was extracted with methyl alcohol and crystallised from light petroleum (b. p. 60—80°) as fine needles (0·2 g.), m. p. 123° (Found: C, 83·9; H, 8·0. Calc. for $C_{14}H_{16}O$: C, 84·0; H, 8·0%). Light absorption: Maxima, 2380 (2780), 2890, 3000, 3300, and 3390 A.; log ε = 4·83 (3·61), 3·73, 3·68, 3·38, and 3·41, respectively. Its *carbanilate* crystallised from alcohol as slender rods, m. p. 138—139° (Found: C, 78·4; H, 6·7. $C_{25}H_{23}O_2N$ requires C, 79·0; H, 6·6%). Its *picrate* crystallised from benzene as red needles, m. p. 130—131° (Found: C, 55·8; H, 4·45. $C_{26}H_{23}O_9N_3$ requires C, 55·9; H, 4·4%).

When the crude α-ethyl-β-(4-methoxy-3 : 5-dimethylbenzoyl)propionic acid (XVII), m. p. 97—107° (6·5 g.), was reduced by amalgamated zinc, the second butyric acid, *β-ethyl-γ-(4-methoxy-2 : 5-dimethylphenyl)butyric acid* was obtained which crystallised from light petroleum (b. p. 40—60°) as prisms (2·1 g.), m. p. 86—87° (Found : C, 71·7; H, 8·6. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). On treatment with 90% sulphuric acid on the boiling water-bath, the preceding compound (2·0 g.) yielded *7-hydroxy-1-keto-5 : 8-dimethyl-3-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* (XIX), which crystallised from 90% alcohol (charcoal) as fine needles (1·3 g.), m. p. 185—186° (Found : C, 76·9; H, 8·2. $C_{15}H_{18}O_2$ requires C, 77·1; H, 8·3%). Its *semicarbazone* crystallised from alcohol as prisms, m. p. 230—231° (Found : C, 65·1; H, 7·5. $C_{16}H_{21}O_2N_3$ requires C, 65·45; H, 7·6%).

The compound (XIX) (0·7 g.) was reduced with amalgamated zinc (20 g.) and concentrated hydrochloric acid (20 c.c.). An oil (0·65 g.) was obtained which was dehydrogenated with selenium (1·8 g.) in the usual way, and the product distilled in steam. The solid obtained was sublimed in a vacuum and crystallised from light petroleum (b. p. 40—60°), yielding *1 : 4-dimethyl-6-ethyl-2-naphthol* (VIII) as radiating needles (0·13 g.), m. p. 92·5° (Found : C, 84·3; H, 7·9. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). Light absorption : Maxima, 2380 (2740), 2840, 2940, and 3360 A.; log ε = 4·85 (3·62), 3·72, 3·65, and 3·46, respectively. Its *carbanilate* crystallised from alcohol as fine needles, m. p. 186—187° (Found : C, 78·6; H, 6·6. $C_{21}H_{21}O_2N$ requires C, 79·0; H, 6·6%).

4-Methyl-7-ethyl-1-naphthol (X).—*Methyl β-(4-ethylbenzoyl)propionate*, obtained from its acid (cf. Levy, *Ann. Chim.*, 1938, **9**, 59), consisted of an oil, b. p. 187—188°/10 mm. (Found : C, 71·1; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). Its constitution was confirmed by oxidation with alkaline hypochlorite to *p*-ethylbenzoic acid.

4-(p-Ethylphenyl)pent-3-enoic acid. A Grignard solution from magnesium (2·3 g.), methyl iodide (12·8 g.), and ether (70 c.c.) was added at 0° to the preceding ester (18 g.), and the mixture was refluxed for 2 hours. After decomposition of the product, the ethereal solution was extracted several times with 12% sodium carbonate solution from which the required *acid* (4·5 g.), m. p. 56—57°, was obtained as silvery plates (from light petroleum) (Found : C, 76·4; H, 7·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

1-Keto-4-methyl-7-ethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. The above unsaturated acid (1·0 g.) was heated with hydriodic acid (7 c.c.) and red phosphorus (1·0 g.) for 6 hours and the product (0·5 g.) heated on the water-bath for 2 hours with a mixture of sulphuric acid (2·5 c.c.) and water (0·5 c.c.). The required tetralone was obtained as an oil (0·2 g.), b. p. 138—139°/1 mm. Its *semicarbazone* separated from alcohol as needles, m. p. 188—189° (Found : C, 68·4; H, 7·5. $C_{14}H_{19}ON_3$ requires C, 68·6; H, 7·8%).

4-Methyl-7-ethyl-1-naphthol (X). The above tetralone (1·0 g.) was brominated and dehydrobrominated as described above, yielding the required *naphthol*, which crystallised from light petroleum (b. p. 40—60°) as sheaves of needles (80 mg.), m. p. 75° (Found : C, 83·8; H, 7·5. $C_{12}H_{14}O$ requires C, 83·9; H, 7·5%). Light absorption : Maxima, 2420, 3040 (3160), and 3310 A.; log ε = 4·57, 3·76 (3·69), and 3·56, respectively. Its *picrate* consisted of scarlet needles (from benzene), m. p. 132—133° (Found : C, 54·95; H, 3·9. $C_{18}H_{17}O_8N_3$ requires C, 54·9; H, 4·1%).

Dehydrogenation of Desmotropo-ψ-santonin.—(+)-β-Desmotropo-ψ-santonin (1 g.) was heated with palladised charcoal (1·25 g.) at 250—280° for 55 hours in a sealed tube. The mixture was then extracted several times with methyl alcohol, and the extract was distilled in steam, yielding a *solid* (II ?) (0·23 g.), m. p. 110—111°. This was sublimed in a vacuum and then crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 113° (Found : C, 84·3, 83·9; H, 7·9, 8·3. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). Light absorption : Maxima, 2420, 3020 (3170), and 3330 A.; log ε = 4·63, 3·69 (3·57), and 3·45, respectively. It formed a *carbanilate*, minute needles, m. p. 150—151° (from dilute alcohol) (Found : C, 78·3; H, 6·8. $C_{21}H_{21}O_2N$ requires C, 79·0; H, 6·6%), *picrate*, dark red needles (from benzene), m. p. 143—144° (Found : C, 55·3; H, 4·3. $C_{20}H_{19}O_8N_3$ requires C, 55·9; H, 4·4%), and *trinitrobenzene* adduct, orange needles (from benzene), m. p. 150—151° (Found : C, 57·8; H, 4·6. $C_{26}H_{19}O_7N_3$ requires C, 58·1; H, 4·6%).

Dehydrogenation of Desmotroposantonin.—(−)-α-Desmotroposantonin (1 g.; m. p. 190°), heated for 40 hours at 240—250° with palladised charcoal (1 g.), yielded *1 : 4-dimethyl-6-ethyl-3-naphthol* (50 mg.) which crystallised from light petroleum (b. p. 120°) as needles, m. p. 123° (compare Bertolo, *loc. cit.*, who gives m. p. 126°) undepressed by the specimen described above.

1 : 4-Dimethyl-2-naphthol obtained by potash fusion of desmotroposantonin (Bertolo, *Gazzetta*, 1902, II, **32**, 374) gave the following light absorption : Maxima, 2360 (2740), 2860, 2970, 3260, and 3380 A.; log ε = 4·75 (3·53), 3·68, 3·65, 3·35, and 3·42, respectively.

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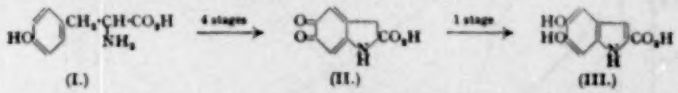
362. *Formation of Tyrosine Melanin. Part II.*

By G. R. Clemo and F. K. Duxbury.

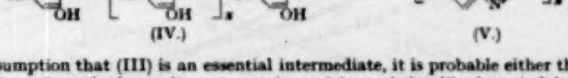
Derivatives of tyrosine and β-phenylalanine have been prepared and their reactions with tyrosinase investigated. The visible and ultra-violet spectra of the resulting pigments have been compared and the results discussed.

Although the formation of melanin from tyrosine has been extensively studied, the reactions involved and the structure of the pigment itself remain unsolved problems. Furthermore, there is still controversy about the relation between natural and synthetic melanins (Mason, *New York Acad. Sci.*, 1948, **4**, 399; Ginsburg, *Genetics*, 1944, **29**, 176). The view that melanin formation from tyrosine (I) involves the five stages needed to convert it into (III) *via* the red pigment (II) was advanced by Raper (*Biochem. J.*, 1927, **21**, 89) and has received confirmation from the spectroscopic work of Mason (*J. Biol. Chem.*, 1948, **172**, 83) and the synthetic work of Robertson and his co-workers (*J.*, 1948, 2223; 1949, 2061).



(I.) (II.) (III.)

Various suggestions have been advanced to account for the formation of melanin from (III), but none has been proved. Clemo and Weiss (*J.*, 1945, 702) suggested that the 5 : 6-dihydroxyindole couples in position 2 and is oxidised at position 3, and that the resulting indigoid structure then undergoes further polymerisation, but this view has been rendered unlikely by Harley-Mason (*J.*, 1948, 1244), who prepared 5 : 6 : 5′ : 6′-tetrahydroxyindigo and found that it did not yield melanin. Burton (*Chem. and Ind.*, 1948, **67**, 313) suggested 4 : 7-coupling of the dihydroxyindole and oxidation at position 3 to give a polymer of the type (IV).



(IV.) (V.)

On the assumption that (III) is an essential intermediate, it is probable either that melanin results from the polymerised coupling at certain positions of the dihydroxyindole system, or that the catechol nucleus first undergoes oxidative fission as postulated by Woodward for the biogenesis of strychnine (*Nature*, 1947, **162**, 155) and by Robinson for that of emetine (*ibid.*, 1948, **162**, 524). If the latter mechanism were involved, (III) would be converted into a reactive ketonic substance and to test this view we added hydroxylamine to the tyrosine enzyme system. The further reaction was not inhibited and we conclude therefore that such an oxidative fission is improbable.

The oxidation of 6-hydroxy-3-phenylindole-2-carboxylic acid to a black pigment led Morton and Slaunwhite (*J. Biol. Chem.*, 1948, **179**, 259) to postulate the quinomethane system (V) for their pigment, which does not need a 5-hydroxyl group.

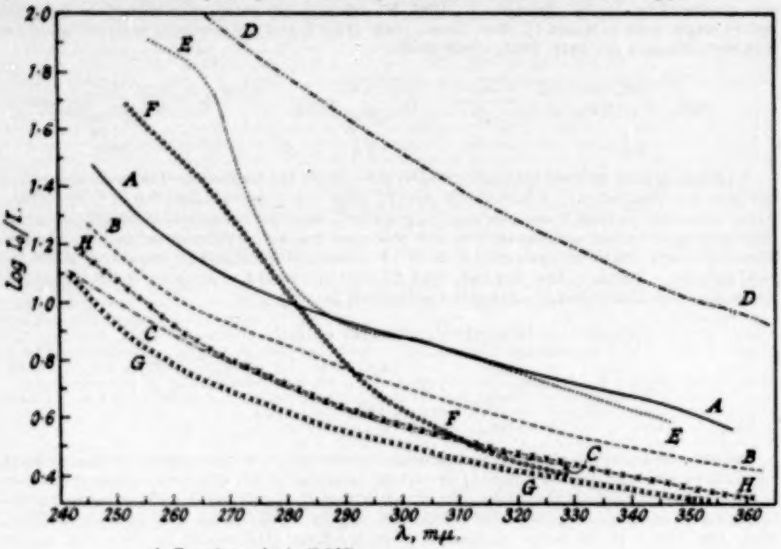
We have therefore based our work on the assumption that the indole nucleus undergoes oxidative coupling at some of the many available centres, and inhibition of melanin formation would be expected if the hydrogen atoms at the active centres were replaced by other groups. Accordingly, substituted tyrosines have been prepared and treated under the standard conditions for production of melanin from tyrosine by tyrosinase. Thus, 2- (Schmalfus and Peschke, *Ber.*, 1929, **62**, 2591) and 3-methyl-, and 3-methoxy-tyrosine yield no melanic pigment, although in all cases position 5 is free for the introduction of the hydroxyl group. The same is true for 2 : 4-dihydroxyphenylalanine (Hirai, *Biochem. Z.*, 1926, **177**, 449), for which the entry of a hydroxyl group at position 5 would be expected to be particularly easy; in this case, however, the enzyme is poisoned, but not in the three cases mentioned above. Although the enzyme is to some extent specific in this reaction the absence of the carboxyl group is stated to produce no difference in melanin formation since tyrosine and p-hydroxyphenylethylamine take up similar amounts of oxygen (Dulière and Raper, *Biochem. J.*, 1930, **24**, 259). The effect of blocking position 2 of the indole nucleus has been examined also by using tyrosine ethyl ester (E. Fischer,

Ber., 1901, **34**, 433). This forms a brown pigment insoluble in aqueous sodium hydrogen carbonate, but readily soluble in warm 10% aqueous sodium hydroxide. The solution yields on acidification a brown solid easily soluble in aqueous sodium hydrogen carbonate with the evolution of carbon dioxide. The ester group has thus been retained.

The ester-containing pigment, unlike tyrosine-melanin, cannot be formed by the autoxidation procedure, which suggests that the dihydroxyindole-2-carboxylic ester is not autoxidised in alkaline solution. The reaction may, therefore, proceed differently from that involved in melanin formation, although Robertson *et al.* (*loc. cit.*) and Burton have shown that a 2-methyl group in the case of 5 : 6-dihydroxy-2-methylindole does not prevent melanin formation.

FIG. 1.

Ultra-violet absorption spectra. Cell length = 1 cm. Concentrations are in mg./ml.



A, *Tyrosine-melanin* (0·066).
B, 2 : 3-*Dihydroxyphenylalanine-melanin* (0·033).
C, *Carboxyl-containing pigment after further enzyme action* (0·030).
D, *Carboxyl-containing pigment* (0·020).
E, *N-Methylmelanin* (0·016).
F, *Adrenalin-melanin* (<0·001).
G, *Tyrosine-melanin* (0·034), *blocked with hydroxylamine.*
H, *Tyrosine-melanin* (0·037), *blank for hydroxylamine test.*

The carboxyl-containing pigment when treated with tyrosinase is converted into a brownish-black pigment initially sparingly soluble, but after reprecipitation insoluble, in aqueous sodium hydrogen carbonate. This slight solubility suggests decarboxylation and the analytical figures suggest that a further reaction has occurred, but since the melanin pigments cannot be purified by recrystallisation—ethylene chlorohydrin, claimed as a suitable solvent by Lea (*Nature*, 1945, **156**, 478), has not proved useful in our hands—the usual analyses cannot be as accurate as for organic compounds generally.

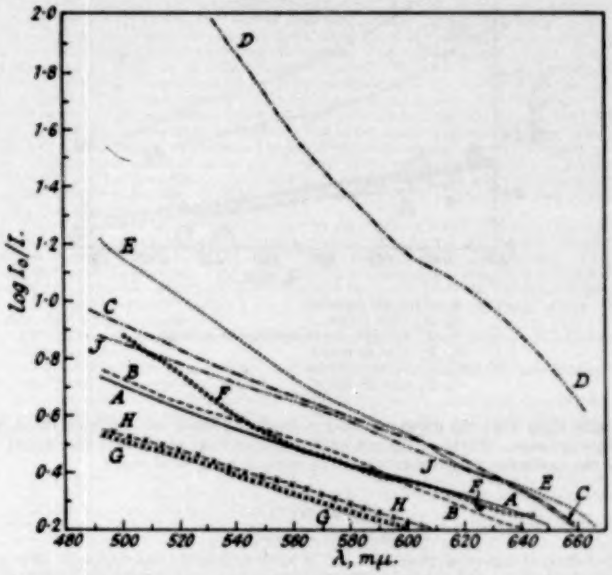
Raper infers that *N*-methyltyrosine (Corti, *Helv. Chim. Acta*, 1949, **32**, 681) forms *N*-methylmelanin which indicates that the blocking of position 1 of the indole nucleus does not inhibit pigment formation and we have found that the ethyl ester of *N*-methyltyrosine, which is blocked in both the 1 and the 2 position yields no pigment. Tyrosine-melanin is only very slightly soluble in aqueous sodium hydroxide after being heated on the water-bath, whereas *N*-methylmelanin as well as the above carboxyl-containing pigment both readily dissolve and

these solutions are thus very suitable for the determination of their visible and ultra-violet spectra (Figs. 1 and 2).

2 : 3-Dihydroxyphenylalanine has also been prepared and found to yield a black pigment easily soluble in N-potassium hydroxide, but not in sodium hydrogen carbonate solution, thus indicating that the 4-hydroxyl group of the indole nucleus is probably free. This pigment is spectroscopically identical with tyrosine-melanin, and this suggests that position 4 may not be needed for polymer coupling as required by Burton's formula.

FIG. 2.

Visible-light absorption spectra. All concentrations are 0·095 mg./ml., except where otherwise stated. Cell length = 2·5 cm.



A, Tyrosine-melanin.
B, 2 : 3-Dihydroxyphenylalanine-melanin.
C, Carboxyl-containing pigment after further enzyme action (0·107).
D, Carboxyl-containing pigment.
E, N-Methylmelanin.
F, Adrenalin-melanin (<0·005).
G, Tyrosine-melanin (blocked with hydroxylamine).
H, Tyrosine-melanin (blank for hydroxylamine test).
J, 2 : 3-Dihydroxyphenylalanine-melanin (substituted indole allowed to autoxidise).

Burton also suggests the introduction of a hydroxyl group at position 3, but we find that adrenalin which has a potential hydroxyl group at position 3 is converted by tyrosinase into a brown pigment spectroscopically different from *N*-methyltyrosine-melanin.

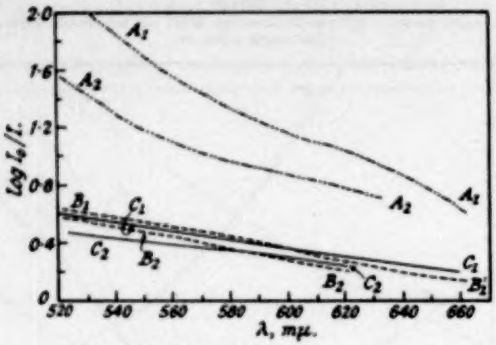
The absorption spectra of the pigments (Figs. 1 and 2) have characteristic gradients. When the solutions are kept in alkaline solution the absorption generally decreases (Fig. 3), no deposit is observed, and the gradient remains constant.

This result is in agreement with Dulière and Raper's observation (*loc. cit.*) that more oxygen is taken up in solutions of pH greater than 8, thus indicating further oxidative coupling whereby the molecular concentration decreases so that absorption becomes less intense. The analytical results obtained for the above-described pigments (dried to constant weight over sulphuric acid in a vacuum) show consistently higher hydrogen values than those quoted previously for melanin and indicate that in all cases formation of the pigment is accompanied by an oxygen uptake.

3-Methoxytyrosine was prepared by a route alternative to that employed by Johnson and Bengis (*J. Amer. Chem. Soc.*, 1913, **35**, 1606). We found the melting point of one of the intermediates, α-oximino-β-(4-hydroxy-3-methoxyphenyl)pyruvic acid, to differ from that recorded by Fischer and Hibbert (*J. Amer. Chem. Soc.*, 1947, **69**, 1208).

FIG. 3.

Visible-light absorption spectra. Decreases in absorption when substances are kept standing in alkaline soln. Concns. as in Fig. 2.



A_1. *Carboxyl pigment.*
A_2. A_1 *after 7 days.*
B_1. *2 : 3-Dihydroxyphenylalanine-melanin.*
B_2. B_1 *after 24 hours.*
C_1. *Tyrosine-melanin.*
C_2. C_1 *after 24 hours.*

Our results show that the pigments from *N*-methyltyrosine and tyrosine ethyl ester differ from tyrosine-melanin. Further, the evidence indicates that positions 1 and 2, but not 4, are involved in the oxidative polymerisation. The work is being continued.

EXPERIMENTAL.

(M. p.s are uncorrected.)

3-Methyltyrosine.—Diketopiperazine (2·0 g.), 4-hydroxy-3-methylbenzaldehyde (4·8 g.), freshly fused sodium acetate (9 g.), and distilled acetic anhydride (9 ml.) were heated for 7 hours at 145—150°. The mixture gradually solidified to a dark brown mass. After addition of water (40 ml.), the cooled product was warmed, filtered, washed with hot water, and recrystallised from acetic acid, *2 : 5-diketo-3 : 6-di-(4-acetoxy-3-methylbenzylidene)piperazine* being obtained as golden-yellow plates (3·9 g., 51%), m. p. 280° (Found : C, 66·5; H, 5·5. $C_{24}H_{22}O_6N_2$ requires C, 66·4; H, 5·1%). The benzylidenepiperazine (1·4 g.), hydriodic acid (22 ml.), and red phosphorus (2·0 g.) were refluxed for 10 hours. The cooled deep-red solution was diluted with water (20 ml.) and filtered, the filtrate evaporated to dryness, water (10 ml.) added, and the yellow solution titrated with aqueous ammonia (*d* 0·986) until the colour just disappeared (pH 5). The free amino-acid was filtered and recrystallised twice from water (charcoal), 3-methyltyrosine being obtained as colourless prisms (0·7 g., 54%), m. p. 276° (Found : C, 61·3; H, 6·7. Calc. for $C_{10}H_{13}O_3N$: C, 61·5; H, 6·7%).

3-Methoxytyrosine.—Sodium (1·7 g.) in absolute ethanol (70 ml.) was added to a warm solution of hydroxylamine hydrochloride (4·8 g.) in the minimum amount of water. After removal of sodium chloride, α-thio-β-(4-hydroxy-3-methoxyphenyl)pyruvic acid (5 g.) was added, the mixture was refluxed for 45 minutes, cooled, and evaporated to dryness in a vacuum. The pale yellow product was dissolved in a minimum amount of aqueous sodium hydroxide (5%), filtered from sulphur, and cooled to 0°. Hydrochloric acid (10%) was added until the solution became pale yellow. α-Oximino-β-(4-hydroxy-3-methoxyphenyl)pyruvic acid slowly crystallised out and was recrystallised from water (yield, 3 g., 60%; m. p. 156°) (Found : C, 53·7; H, 5·2. Calc. for $C_{10}H_{11}O_5N$: C, 53·3; H, 4·9%). To the oximino-acid (4 g.) in aqueous sodium hydroxide (8%; 30 ml.) sodium amalgam (4%; 80 g.) was added during 30 minutes. The solution was evaporated to 30 ml., treated with charcoal, and cooled. The amino-acid was filtered off, dried at 100°, and recrystallised from water. 3-Methoxytyrosine was obtained as colourless prisms (3·1 g., 80%), m. p. 257° (Found : C, 48·4; H, 6·9. Calc. for $C_{10}H_{13}O_4N,2H_2O$: C, 48·6; H, 6·9%. Found, after drying in a vacuum at 100° : C, 56·8; H, 6·6. Calc. for $C_{10}H_{13}O_4N$: C, 56·9; H, 6·2%).

Ethyl Ester of L-*N-Methyltyrosine.*—L-*N*-Methyltyrosine (3 g.) was dissolved in ethanol (20 ml.), the cooled solution saturated with hydrogen chloride, ethanol (42 ml.) added, the whole refluxed for 7 hours and then evaporated to dryness in a vacuum, and the residue dissolved in water (20 ml.). The solution was neutralised (potassium carbonate) and extracted with ethyl acetate, the solvent removed, and the *ethyl* ester distilled (b. p. 158—162°/2 mm.) as a colourless oil which solidified and recrystallised from ethyl acetate in colourless prisms, (2·0 g., 59%), m. p. 122° (Found : C, 64·7; H, 7·3. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·6%).

α-Amino-β-(2 : 3-dihydroxyphenyl)propionic Acid.—o-Vanillin (5 g.), hippuric acid (6·2 g.), anhydrous sodium acetate (3·0 g.), and acetic anhydride (10·3 ml.) were heated on a water-bath for 30 minutes. The mixture gradually solidified. Water (25 ml.) was added and the yellow product warmed, filtered off, washed with hot water, and recrystallised from absolute ethanol. The *azlactone* of α-benzamido-β-(3-acetoxy-3-methoxyphenyl)cinnamic acid was obtained as yellow needles, (9 g., 82%), m. p. 156—157° (Found : C, 67·7; H, 4·7. $C_{19}H_{15}O_5N$ requires C, 67·7; H, 4·4%).

A solution of the azlactone (5 g.) and sodium hydroxide (1·8 g.) in 50% ethanol (75 ml.) was warmed for 15 minutes, water (150 ml.) added to the deep-red solution, and hydrochloric acid (20%) added dropwise with stirring until the acid was precipitated and the solution assumed a pale yellow colour. The *α-benzamido-β-(2-hydroxy-3-methoxyphenyl)cinnamic acid* recrystallised from 75% ethanol in colourless plates (3·2 g., 74%), m. p. 226° (Found : C, 65·7; H, 4·8. $C_{17}H_{15}O_5N$ requires C, 65·2; H, 4·8%). The recrystallised cinnamic acid (2·5 g.), hydriodic acid (15 ml. ; *d* 1·7), acetic anhydride (15 ml.), and red phosphorus (1·5 g.) were refluxed under hydrogen for 2½ hours. Water (30 ml.) was added, the phosphorus and some benzoic acid were filtered off, the yellow filtrate was extracted 3 times with ether, and the aqueous layer evaporated under hydrogen. The clear brown residual oil was dissolved in water (20 ml.) containing a little sulphur dioxide and treated with charcoal, and the resulting pale yellow solution was treated dropwise with aqueous ammonia (*d* 0·986) till it became green and commenced to darken. The α-amino-β-(2 : 3-dihydroxyphenyl)propionic acid was filtered off and twice recrystallised from aqueous sulphur dioxide (charcoal), forming colourless prisms (1·2 g., 71%), m. p. 265° (Found : C, 55·0; H, 5·8. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6%).

Melanin Formation.—The amino-acid (0·1 g.) was dissolved in water (200 ml.), the enzyme solution (10 ml.) (Raper, *loc. cit.*) and phosphate buffer (5 ml. ; pH 8) were added, and air was bubbled through the solution for 24 hours. 3-Methoxy- and 3-methyl-tyrosine produced no pigment. 2 : 4-Dihydroxyphenylalanine poisoned the enzyme. The ethyl ester of L-*N*-methyltyrosine gave a yellow-green deposit. The ethyl ester of L-tyrosine produced a brown pigment different from the black one from L-*N*-methyltyrosine. 2 : 3-Dihydroxyphenylalanine gave a deep-maroon-coloured solution, which after 24 hours gradually deposited a black pigment.

In the cases where no pigment was formed, tyrosine (0·1 g.) in water (40 ml.) was subsequently added, to check the enzyme activity.

The autoxidation procedure employed by Raper (*Biochem. J.*, 1925, **19**, 90) was applied to L-tyrosine ethyl ester and 2 : 3-dihydroxyphenylalanine.

A solution of the amino-acid (or ester) (0·2 g.), water (400 ml.), and enzyme solution (20 ml.) was oxygenated until the red colour was a maximum : 2 hours for the ester, 4 hours for the acid. The solution was acidified (10% acetic acid ; 8 ml.) and boiled. The precipitated products were filtered off and the colourless filtrate treated with aqueous sodium carbonate (10% ; 10 ml.). The mixture was shaken with air for 24 hours.

2 : 3-Dihydroxyphenylalanine yielded a black pigment, similar to the above. Tyrosine ethyl ester yielded a reddish solution ; this was treated with enzyme solution (20 ml.) and oxygenated ; the ester-containing pigment was then deposited.

Carboxyl-containing Pigment.—The ethyl tyrosine ester-melanin was centrifuged with other biological impurities, and the brown solid treated with aqueous potassium hydroxide (20 ml. ; 10%) and warmed on a water-bath for 30 minutes. The solution was centrifuged till no more deposit was observed and then acidified (10% hydrochloric acid). The free acid was centrifuged off, redissolved in 2% sodium hydrogen carbonate solution, filtered, centrifuged, and re-acidified. The process was repeated twice, and the pigment well washed with distilled water (Found : C, 51·9, 52·5 ; H, 5·2, 5·8 ; N, 9·3, 9·4%).

Alkaline hydrogen peroxide bleached the pigment and reduction with Raney nickel alloy in sodium hydroxide solution gave a pale brown solution similar to that obtained from melanin. On treatment with tyrosinase, the acid yields a brownish-black pigment sparingly soluble in 2% sodium hydrogen carbonate solution. After reprecipitation from the latter it is insoluble in aqueous sodium hydrogen carbonate, but soluble in sodium hydroxide (Found : C, 50·0, 49·8 ; H, 5·4, 5·6 ; N, 10·4, 10·8%).

2 : 3-*Dihydroxyphenylalanine-melanin.*—2 : 3-Dihydroxyphenylalanine on treatment with tyrosinase formed a black pigment. Its properties were similar to those of tyrosine-melanin, except that it was soluble in cold N-potassium hydroxide. Purification was effected by using the autoxidation procedure and then proceeding as described for the carboxyl-containing pigment. N-Potassium hydroxide was used instead of sodium hydrogen carbonate solution (Found : C, 59·7, 59·2 ; H, 4·9, 5·4 ; N, 8·1, 8·4%).

Adrenalin-melanin.—Adrenalin hydrochloride (20 mg.), water (40 ml.), enzyme solution (2 ml.), and buffer solution (1·5 ml.) were oxygenated for 24 hours. The brownish-black pigment deposited was centrifuged off and purified as above. It was soluble in cold N-potassium hydroxide. Purification was effected as above.

Melanin Formation in the Presence of Ketonic Reagents.—A mixture of tyrosine (0·1 g.) in water (200 ml.) and enzyme solution (10 ml.) was oxygenated until the deep-red coloration was observed (3—4 hours). The solution was acidified (10% acetic acid ; 4 ml.) and boiled. The precipitated biological products were filtered off, and the colourless filtrate (stable in acid solution) was treated with a solution of hydroxylamine hydrochloride (0·5 g.) and sodium carbonate (1·2 g.) in the minimum amount of water.

Slight melanin formation was observed before the addition of alkali. 2 : 4-Dinitrophenylhydrazine (0·2 g.) and dimedone (0·1 g.) were added to separate portions of the acid solution. Pigment formation was still observed, although acid conditions are not favourable for melanin formation.

Determination of Spectra.—All the absorption spectra were observed by use of the Hilger Medium

Quarts Spectrograph and the Hilger Nutting Spectrophotometer. N-Potassium hydroxide was the solvent.

One of us (F. K. D.) thanks the Council of King's College for the award of a Research Studentship and the Department of Scientific and Industrial Research for a maintenance allowance.

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KING'S COLLEGE, NEWCASTLE UPON TYNE. [*Received, March 16th*, 1950.]

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363. *The Kinetics of the Decomposition of Nickel Formate.*

By L. L. BIRCUMSHAW and JOSEPH EDWARDS.

Accurate analysis of the gases evolved when anhydrous nickel formate is heated *in vacuo* at 165—180° indicates that the reaction is represented mainly by the equation :

$$2(H\text{-}CO_2)_2Ni \longrightarrow 2Ni + 3CO_2 + CO + H_2 + H_2O$$

The rate of the thermal decomposition of this salt has been investigated in this temperature range, as well as the influence on the decomposition of (1) spreading the material, (2) allowing the gaseous products to accumulate, (3) preliminary grinding of the salt, (4) mixing the salt with the solid residue, and (5) interrupting the reaction.

The decomposition follows the Prout–Tompkins relationship, $\log (p/p_f - p) = kt +$ constant, if the salt is "spread." The solid product catalyses the reaction, and the gaseous products have a considerable inhibiting effect. Water vapour is particularly important in this respect, especially in connection with the induction period and the initial stages of the reaction.

IN spite of the importance of nickel formate as a source of active nickel for use in a number of catalytic processes, little appears to be known of the manner in which it decomposes. Caujolle (*Compt. rend.*, 1939, **204**, 445) heated its dihydrate in a vacuum, raising the temperature gradually to 300°. The gaseous products evolved were collected in two fractions between 100° and 200° and 200° and 300° and analysed separately. The greater part of the gas was evolved between 200° and 300° but the compositions of both fractions were similar. The residue was entirely metallic nickel and a certain amount of methane appeared if the decomposition was carried out at higher temperatures. Balandin, Gregorian, and Janischeva (*J. Gen. Chem. Russia*, 1940, **10**, 1031) from a study of the decomposition between 215° and 270° considered that the two reactions

$$(H\text{-}CO_2)_2Ni \longrightarrow \begin{cases} Ni + H_2 + 2CO_2 & \ldots\ldots\ldots (a) \\ Ni + H_2O + CO + CO_2 & \ldots\ldots\ldots (b) \end{cases}$$

proceed simultaneously until 40—50% has decomposed, after which only reaction (*a*) persists. The decomposition was carried out in air, in nitrogen, and in oil. The nickel residue obtained in air or nitrogen was almost completely catalytically inactive, but that obtained in oil was extremely active. If the gaseous products were left in contact with the residue a slow contraction (about 5%) took place, owing to the catalytic formation of methane from the carbon monoxide and hydrogen. Dobytshin and Zelmskaja (*Bull. Inst. Chem. Phys.*, 1938; but see also Roginsky, *Trans. Faraday Soc.*, 1938, **34**, 959) believed the decomposition to proceed according to equation (*a*). Unfortunately, we do not know the exact conditions under which their experiments were carried out, as their paper could not be obtained. Clearly, the course of the thermal decomposition of nickel formate had to be clarified as an essential preliminary to any work on the kinetics.

Analyses of the gases produced at four different temperatures (105—180°) were carried out. The effect of varying the rate at which gas is pumped off from the decomposing solid was investigated—also that of leaving the gas in contact with the solid residue for varying periods of time. Since even the most rapid rate of pumping with a Toepler pump does not compare with that of the pumping unit in the kinetics experiments the effect of removing carbon dioxide and water by means of a liquid-oxygen trap while pumping (with the Toepler pump) as quickly as possible was also tested. The weight and appearance of the residue were noted in each experiment.

EXPERIMENTAL.

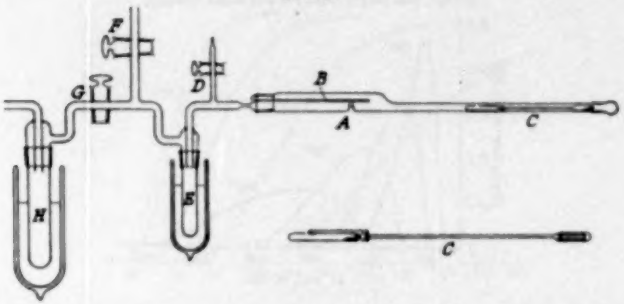
As nickel formate dihydrate is almost equally soluble in hot and in cold water, it was necessary to obtain the substance by careful evaporation of a solution. "AnalaR" Nickel carbonate (20 g.) was added, in small portions, to a solution (500 ml.) containing an excess of formic acid (if sufficient formic

acid is not present a formo-carbonate may be produced). The resulting solution was filtered and then evaporated slowly to about one-third of its bulk. After the mixture had been cooled and kept overnight the dihydrate was filtered off and washed with distilled water until no smell of formic acid could be detected. The salt was then recrystallised twice in the same way, dried in a vacuum desiccator, and stored in a desiccator containing no drying agent. Thus prepared the dihydrate was a very fine green powder which was seen under a microscope to consist of very small crystals. The nickel content (Found : Ni, 31·6. Calc. for $C_2H_2O_4N,2H_2O$: Ni, 31·9%) was determined by the dimethylglyoxime method.

The gases were usually collected by use of a decomposition tube of the type shown (Fig. 1), which was used for the kinetic experiments. A constriction on the tube ensures that the salt is always in the same position relatively to the thermocouple in *B*. The formate was introduced by means of a permanent magnet and a glass rod attached to a tube containing a small piece of iron (*C*). The enlarged view of *C* shows the arrangement for interrupting the decomposition : a platinum wire attached to the glass rod by a wire collar engages the hole in the small tube making it possible to withdraw it by means of the magnet. With this arrangement part of the rod must remain in the furnace during the decomposition. It was found, however, to have no great effect on the course of the reaction though it did take slightly longer to attain a constant temperature. The water formed is condensed in *E*, surrounded by solid carbon dioxide and alcohol. The apparatus is evacuated through *I* which is connected to a mercury trap, a two-stage mercury-vapour pump, and a Cenco oil pump. A liquid-oxygen trap *H* is included and the whole apparatus is made of wide-bore Pyrex tubing to ensure rapid evacuation. The rate of decomposition is measured by cutting off the pumps (*i.e.*, closing tap *G*) at fixed intervals, allowing the pressure to rise for 30 seconds, and measuring it in a McLeod gauge connected through *F*. *D* is a leak tap. The gas collected over the Toepler pump was analysed in an Ambler gas-analysis apparatus.

In the few experiments in which the products were allowed to accumulate the volume of the apparatus was increased by attaching bulbs of various sizes to the end of the decomposition tube.

FIG. 1.



After a few preliminary experiments had been made on the kinetics of the decomposition it became important to discover the precise effect of variations of temperature, rate of pumping, etc., and a more thorough investigation was carried out.

Decomposition was carried out at the four temperatures used in the kinetical work, *viz.*, 165°, 170,° 175°, and 180°. With a " normal " rate of pumping—one stroke of the Toepler pump per minute—the compositions of the gases at the four temperatures were compared. Then at 180° experiments were made to test the effect of pumping at two strokes per minute. Since this rate of removal of the product gases did not compare with that in the kinetical experiments, a run was performed with liquid oxygen around the trap *E* instead of solid carbon dioxide and alcohol. This, of course, removed the carbon dioxide as well as the water. When decomposition was complete the liquid oxygen was replaced by carbon dioxide–alcohol, the remaining gas was pumped off, and the total gas analysed.

The effect of leaving the gases produced in contact with the nickel residue was next investigated. Since the volume of the apparatus was comparatively small, the final pressure attained was considerable, and any reaction caused catalytically by the nickel should certainly be apparent. To decide whether the reaction is the same over the whole course of the decomposition, the gases produced in one run were collected in fractions corresponding roughly to the first and the second half of the decomposition.

The most important point emerging from these experiments is that the variations in composition of the gases under the different conditions are very small indeed. No methane was detected in any of the samples but this is not surprising in view of the low temperature.

The mean result (excluding those of the incomplete accumulated-pressure run and the broken run) is:

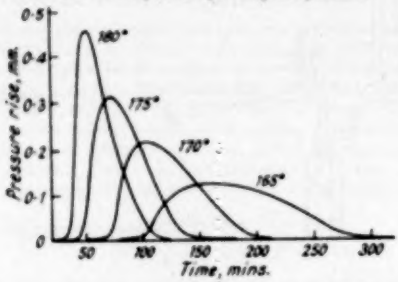
	Ml. from 40 mg.	%	Litres/g.-mol.	
CO_2	7·28 (7·28)	60·9 (60·0)	33·6 (33·6)	
CO	2·29 (2·42)	19·2 (20·0)	10·6 (11·2)	(Mean wt. of residue = 0·0128 g.)
H_2	2·38 (2·42)	19·9 (20·0)	11·0 (11·2)	
Total	11·95 (12·12)	100·0 (100·0)	55·2 (56·0)	

If the two processes (*a*) and (*b*) (p. 1800) play an equal part in the reaction the theoretical values should be those shown in parentheses above The conclusion can be drawn that nickel formate decomposes at 165—180° according to the reaction $2(H{\cdot}CO_2)_2Ni \longrightarrow 2Ni + 3CO_2 + CO + H_2 + H_2O$, and that variation in the rate of removal of the gas from the salt or leaving the product gases in contact with the residual nickel has little effect.

The Kinetics of the Decomposition.—The current in the furnace winding was increased for a minute or two before introduction of the salt into the furnace. After a little practice it was possible, in this way, to raise the salt to the temperature required in a very short time. In all experiments the same amount of salt (40 mg. of the dihydrate) was used. Before an experiment was begun, the apparatus was evacuated for one hour and tested for leaks. As the tube was pushed into the furnace by means of a magnet a stop-watch was started. At intervals of 5 minutes (or 2½ minutes where the rate was changing very rapidly) the pumps were cut off and

FIG. 2.

30-Sec. rise in pressure for unspread formate.



the pressure inside the apparatus was allowed to rise for 30 seconds. The pressure was then read on a McLeod gauge. This pressure is a measure of the rate at which the decomposition is proceeding, the actual value depending of course on the volume of the apparatus and the amount of salt taken. Twice this value was taken as $d\rho/dt$, the pressure rise in unit time (1 minute).

In the runs with the " unspread " formate the salt was shaken into a small heap at the end of the tube but was not allowed to block the whole width of the tube. If it did so, it tended to be blown along the tube as the decomposition proceeded. The best method for the preliminary dehydration was heating in air at 130—135°, and this method was adopted for all the work.

Typical rate–time curves are shown in Fig. 2. In every case there is an induction period which is greater at the lower temperatures. The maximum rate is about 0·46 (in these arbitrary units) after 50 minutes at 180° and 0·125 after 155 minutes at 165°. The curves are typical of a number of solid decompositions in which the rate, after an induction period, accelerates to a maximum and finally falls to zero. The curve in this case is not symmetrical, the rise to the maximum being steeper than the fall to zero.

The total pressure at any time, *i.e.*, the pressure which would have been obtained had the pumps been permanently cut out and the pressure allowed to rise, is proportional to the amount of nickel formate decomposed and can be evaluated by square counting: the area enclosed by the curve and the time axis represents the amount of decomposition which has taken place and is proportional to the total pressure at that time. It is possible, of course, to make direct measurements of p and this was done later. The present method, however, eliminates the retarding effect (if any) of increasing pressure of product gases. Two of the rate–time curves at each of the four temperatures were plotted and integrated by the method of square counting,

so that the values of p at each interval were obtained. The pressure–time curves plotted in Fig. 3 have the well-known sigmoid shape. At all four temperatures the maximum rate occurs when the decomposition is about one-third completed.

With the values for dp/dt and the corresponding values for p at the various temperatures we can test the applicability of various equations which have been put forward to account for the course of solid decompositions. We have first

$$dp/dt = kt^m \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$dp/dt = kp^{2/3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Both these equations are deduced on the assumption that the reaction spreads spherically into the body of the decomposing solid. Garner has shown that the maximum value of m should be 3·0. Equation (2) involves the assumptions of the simple interface theory. In addition we have the well-known equations derived from the branching theory :

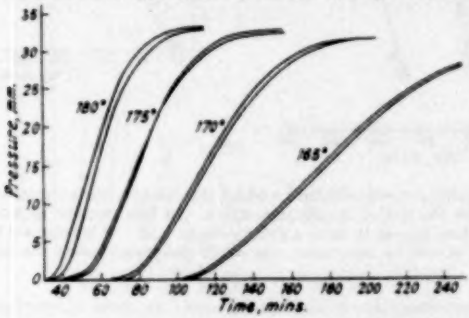
$$\ln p = k_3 t + \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\ln dp/dt = k_4 t + \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

A plot of log (dp/dt) against log p does not give a straight line. This being so, and as m always exceeds 3·0, it appears that the simple interface theory does not apply in the normal decomposition.

FIG. 3.

Total pressure–time curves by integration of rate–time curves for unspread formate.



It is often found in solid decompositions which occur with evolution of a gas that the pressure increases exponentially with time. The decomposition of anhydrous nickel formate is no exception. As can be seen from Fig. 4, equation (3) is obeyed practically up to the time of maximum rate. The values of the constants k_3 are :

Temp.	165°	170°	175°	180°
k_3	0·079	0·107	0·162	0·208

The branching-chain equation (4) has been found to apply in many cases where the exponential equation holds. Plotting log dp/dt against t gives straight lines for the initial part of the decomposition at all four temperatures but the relation breaks down before the maximum rate of decomposition is reached, k_4 being :

Temp.	165°	170°	175°	180°
k_4	0·0563	0·128	0·169	0·265

It should be noted that equations (3) and (4) are, except for the integration constant, identical, *i.e.*, k_3 should be equal to k_4.

The final stages of the decomposition do not follow a first-order law

$$k_1 = [1/(t_2 - t_1)] \ln (p_f - p_{t_1})/(p_f - p_{t_2})$$

where p_f is the total final pressure.

In their work on the thermal decomposition of potassium permanganate (*Trans. Faraday Soc.*, 1944, **40**, 488), Prout and Tompkins concluded that the whole course of the decomposition

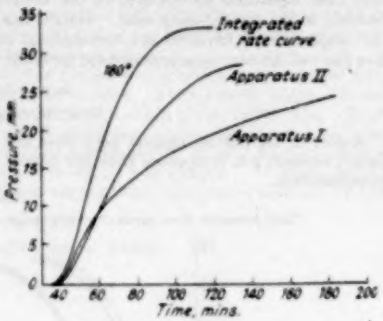
could be expressed by the equation $\log p/(p_f - p) = kt + \text{constant}$, where k has two different values before and after the time of maximum rate. This has been found to apply in a number of other decompositions and has been tested with the present results. The agreement with the equation is only moderate. The graphs are continuous curves which only approximate to

FIG. 4.

log p–t for unspread formats.

FIG. 5.

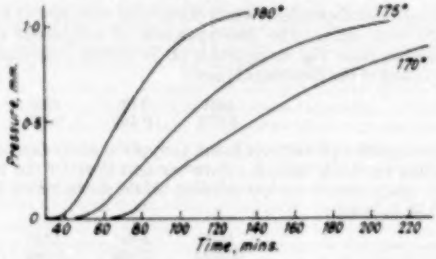
Total pressure–time for unspread formats.



straight lines. In other decompositions, for which this relation holds approximately, a departure often occurs towards the end of the decomposition. In this case the departure is particularly marked and the values appear to lie in a third straight line. It is pointless to speculate on the cause of this and, as will be seen later, the effect disappears when the salt is spread. The

FIG. 6.

Total pressure–time curves by direct measurement—Apparatus II, unspread formats.



intersection of the lines corresponding to the acceleration and the decay of the reaction is seen in each case to occur slightly before the time of maximum rate.

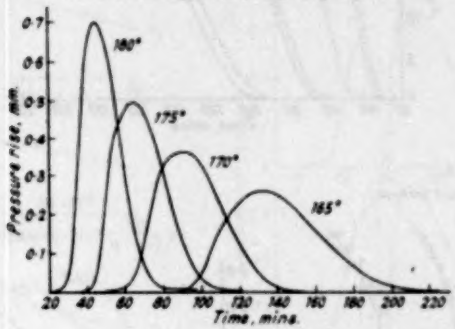
The Effect of Allowing the Products of Decomposition to Accumulate in the Apparatus.—This effect has been studied by making a number of experiments in which the pumps were cut off permanently and the pressure allowed to rise in the apparatus. It was advisable to retain the same quantity of material and hence to ensure that the pressures developed could be measured on the McLeod gauge the volume of the apparatus had to be increased. This was done in the first case (apparatus I) by attaching a 1-litre bulb, through a tap and Quickfit joint, to the end of

the decomposition tube. The ratio of the volumes, with and without the bulb, was measured by allowing a little air to enter the evacuated apparatus and reading the pressure. The tap connecting with the bulb was then opened and the pressure read again. The ratio of the former to the latter pressure gave the conversion factor. A plot of the results obtained, corrected for the volume increase at 180°, is seen in Fig. 5. It will be noticed that the pressure produced has a strong retarding effect on the reaction, so much so that the complete decomposition even at 180° takes more than 4 hours. Experiments were also made on an apparatus with a volume further increased. Six 1-litre bulbs were added in this case, and experiments were made at 180°, 175°, and 170°.

The results are shown graphically in Fig. 6. It will be noticed in Fig. 5 that there is a difference in final pressure between apparatus I (28·12 mm.), apparatus II (28·50 mm.) and the integrated rate curve (33·13 mm.). This is due to the presence of water vapour in the products of decomposition. The magnitude of the difference indicates that even when a carbon dioxide–alcohol trap is included in the system the rate of condensation of water is much slower than its rate of production, so that part of the pressure recorded is due to some water vapour. The final pressure reading in the direct p–t measurement does not of course include any water vapour. According to the equation deduced for the reactions, the volume of water vapour

FIG. 7.

30-Sec. rise in pressure for spread formate.



should be one-fifth of the sum of the other gases, and the difference in the final pressure (integrated) is about one-sixth of the " accumulated " pressures (no water). Thus it appears that in the 30 seconds only a small fraction of the water vapour is condensed in the trap. If we make the highly probable assumption that the rate of condensation at any moment is proportional to the pressure of water vapour present (during the 30-second intervals), at least over the range investigated, then the integrated p's are still proportional to the actual rate of decomposition of the nickel formate. The rates of production of water vapour are widely different at the different temperatures, yet the fractional differences between final pressures (integrated and " accumulated " pressures) remain sensibly the same.

Effect of Spreading the Nickel Formate.—In connection with the work described in the last section (direct total pressure measurements) it was decided to make experiments, in the same apparatus, with smaller quantities of formate. In an exploratory run, however, small decomposed much more rapidly than larger quantities. This raised the question of the effect of spreading on the rate of decomposition, since the increase in rate with smaller quantities may be due to the diminished resistance offered to the escape of gases by the solid product. The rate of decomposition of the spread salt was, in fact, found to be considerably greater than that of the unspread. The rates were therefore investigated at the four temperatures, the formate being spread out along the whole length (about 4 cm.) of the small tube. The rate–time curves are given in Fig. 7. The increase in maximum rate over the unspread salt varies between 50 and 100% and is greatest at the lowest temperature. The total pressures were evaluated by graphical integration and the pressure–time curves for the four temperatures are shown in Fig. 8.

As with the unspread salt, the value of n derived from the equation (1) exceeded 3·0, and a

plot of log dp/dt against log p did not give a straight line, so the simple interface theory does not apply. Both the exponential and the branching-chain equations hold over the first part of the decompositions (Fig. 9). The constants k_1 and k_2 are given below, agreement being excellent.

Temp.	165°	170°	175°	180°
k_1	0·102	0·132	0·189	0·249
k_2	0·098	0·125	0·190	0·246

FIG. 8.

Total pressure–time curves by integration of rate–time curves for spread formate.

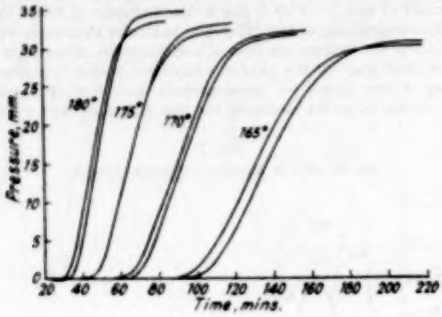


FIG. 9.

log p–t for spread formate.

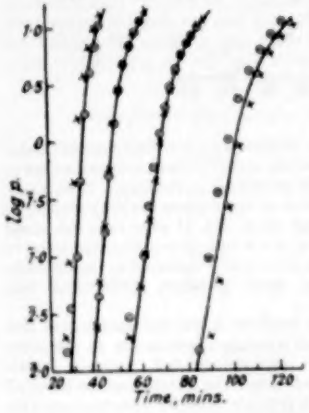
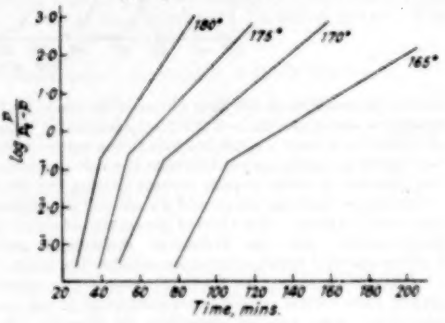


FIG. 10.

log $\frac{p}{p_1 - p}$–t for spread formate B.



Very good agreement is also obtained with the Prout–Tompkins equation. Two straight lines account for the whole course of the reaction at all temperatures (see Fig. 10). The intersection of these lines is still, however, as with the unspread salt, before the time of maximum rate. The mean constants k_a and k_b are :

Temp.	165°	170°	175°	180°
k_a	0·093	0·122	0·173	0·2215
k_b	0·030	0·042	0·056	0·0747

The plot of log k in each case against $1/T$ is shown in Fig. 11, and E calculated from the four slopes is: k_1 22,900, k_2 20,100, k_4 23,800, and k_5 24,100 cals. (mean 22,700). This may be compared with the value (26,400 cals.) for E for the unspread salt.

The Effect of Grinding the Formate before Decomposition.—The preliminary grinding of solids before decomposition generally modifies the rate of reaction (by reducing the particle size) and almost eliminates any induction period (by increasing the rate of nucleation). The particle size of anhydrous nickel formate is already very small, and it seemed possible that the rate of decomposition would not be greatly altered by grinding. This was tested experimentally. Ordinary dry grinding was found to be most unsatisfactory. The formate was compressed into lumps which decomposed very irregularly. Grinding was therefore carried out with an agate pestle and mortar under carefully dried carbon tetrachloride (1) before dehydration and (2) after dehydration, and also (3) one sample of the salt was treated with carbon tetrachloride without grinding. In no case was any noticeable effect on the rate observed, nor was the induction period removed.

FIG. 11.

log k–1/T for spread formate.

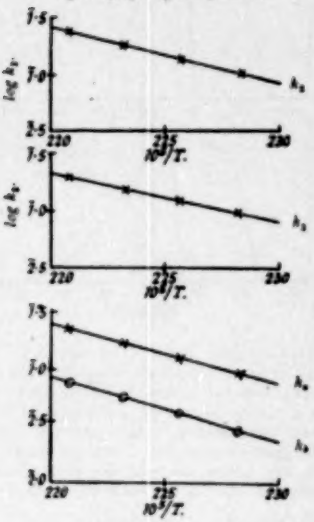
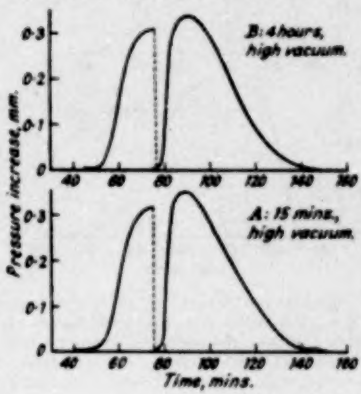


FIG. 12.

Interrupted runs, unspread formate at 175°.



The Effect of the Nickel Residue on the Decomposition.—In a number of solid decompositions, the reaction, after the time of maximum rate, follows a first-order law. In others, however, the solid product catalyses the reaction. In their study of the decomposition of potassium permanganate Prout and Tompkins assume this to be so when deriving their equation. Since the Prout–Tompkins equation holds for the decomposition of the present substance, it seemed likely that the nickel residue was capable of catalysing the reaction. Direct observation of partially decomposed material in which decomposition was seen to have occurred in patches confirmed this.

Direct experiment with the usual quantity of dehydrated salt mixed with the entire residue from a previous run showed that the decomposition followed a normal course for about 20 minutes and then suddenly accelerated, reaching a maximum rate higher than that of a normal run. The rate then dropped rapidly but the final stages of the decomposition appeared to be slower than usual. The induction period remained practically unchanged. However, the mixing may be uneven, and simple contact may not be sufficient for pronounced catalysis; also the bulk of the material is almost doubled, so it is difficult to compare the extent to which the

formate itself is spread, and the gases produced must escape through a solid layer containing a higher proportion of residue.

Interruption of the Reaction.—It was obviously valueless to interrupt the reaction at a point where the rate was changing rapidly, so the decomposing salt was in each case withdrawn from the furnace as nearly as possible at the time of maximum rate. The solid was allowed to cool in a high vacuum or in air for various times. In view of the influence of water vapour on the induction period (see next section) experiments were also made in which the solid was allowed to cool in (1) dry air and (2) water vapour. In the latter case, after withdrawal of the solid, the pumps were cut off and the liquid oxygen was removed from a trap in the system which contained a little water. Before continuing the decomposition, of course, the apparatus was completely evacuated. All the experiments were made at 175° and results are given in Figs. 12 13 and 14.

FIG. 13.

Interrupted runs, unspread formate at 175°.

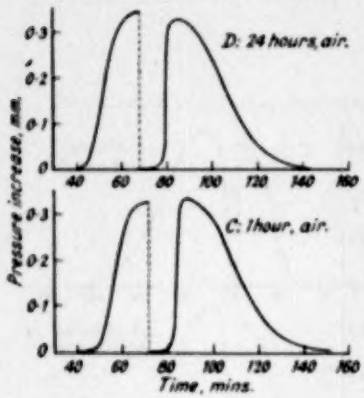
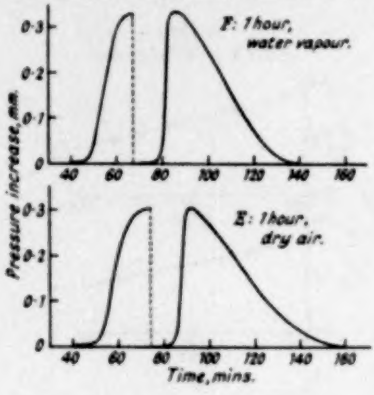


FIG. 14.

Interrupted runs, unspread formate at 175°.



They fall into two groups : (1) those with cooling in a high vacuum, and (2) the remainder. In the first, the reaction continues immediately after the interruption, as before, if we allow for the short time it takes the sample to become heated. The maximum rate attained after interruption is slightly higher than usual. This is probably due to a slight spreading due to moving the tube in and out of the furnace. In the other four experiments there is an induction period of about ten minutes before the reaction begins again. The rate then rises rapidly to the maximum—more rapidly than before, since in this case the sample will, during the induction period, have attained the temperature of the furnace. The maximum attained is the same as the original maximum.

The temporary inhibition of the reaction in the presence of adsorbed water vapour is important. Apparently, the interface is completely poisoned by adsorbed gas and the reaction can only proceed when the gas has been removed. There is a possibility that the effect is produced by water vapour; under the conditions of the experiment, the dried air might contain a trace of water vapour, enough to inhibit the decomposition.

The Induction Period.—The induction period becomes shorter with rise of temperature. The values of t_0, the induction period, and $\log 1/t_0$ for the various temperatures are given below :

Temp.		165°	170°	175°	180°
Unspread	t_0	80	52·5	35	25
	$\log 1/t_0$	2·097	2·280	2·456	2·602
Spread	t_0	70	45	30	20
	$\log 1/t_0$	2·155	2·347	2·522	2·699

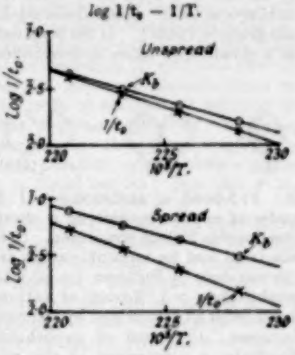
The values are plotted along with the corresponding values of k_0—probably the most reliable of the rate constants. The points lie quite close to a straight line in each case, and it will be seen that the slope and therefore the activation energy of the induction process is of the same order as that of the decomposition itself (Fig. 15).

Some experiments were made to test the effect of interrupting the induction period. Samples of unspread formate were heated *in vacuo* at 165° for 60 minutes, withdrawn from the furnace, allowed to cool for a time, and then returned to the furnace, and the length of the induction period was measured. This period was found to depend on the conditions of cooling:

	(1)	(2)	(3)	(4)	(5)
Conditions of cooling	1 hour, high vac.	5 hours, high vac.	24 hours, high vac.	1 hour, air	24 hours, air
t_0 after interruption	25	25	35	80	80
	(6)	(7)	(8)	(9)	
Conditions of cooling	1 hour, water vap.	24 hours, water vap.	1 hour, dry air	5 hours, dry air	
t_0 after interruption	80	80	30	40	

These results appear to show that whatever occurs during the induction period persists through an interruption if it takes place in the absence of water vapour. When the latter is present, however, the complete induction period is restored. Small amounts of water vapour are undoubtedly responsible for the slight increase of t_0 in (3) and (9).

FIG. 15.
log $1/t_0 - 1/T$.



It might seem that the induction period is simply a period of desiccation necessary before any decomposition can take place. It must be remembered, however, that water is one of the products of the decomposition and hence complete desiccation at a temperature at which decomposition can take place is not possible. Further, the length of time a sample is left in the drying oven (at 130°) or in the evacuated apparatus (at room temperatures) before decomposition has no effect on t_0. Hence, the induction period is not the consequence of water originally present in the salt. It is probable that decomposition begins as soon as a sample is introduced into the furnace. Acceleration is slow since the nuclei are small and because gaseous products (probably water is the most important) tend to depress the rate of reaction. If the products are removed more quickly the acceleration is increased. Thus spreading reduces t_0 a little, and the addition of a layer of residue increases it. At time t_0 the rate of decomposition becomes measurable, and shortly afterwards a rapid acceleration occurs, presumably when the nuclei reach a certain size. Since cooling in water vapour restores the full induction period, it must be assumed that a sufficient concentration of water is able to poison completely those nuclei which have already begun to grow.

One of us (J. E.) thanks the University of Birmingham for the award of a University Research Scholarship.

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364. *The Relative Reactivity of Aromatic Double Bonds. Part III. The Relation between Double-bond Character and the Velocity of Addition of Osmium Tetroxide.*

By G. M. BADGER.

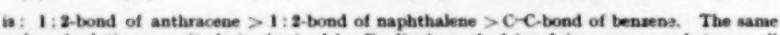
The relation between the double-bond character, or order of a bond, and the velocity of addition reactions is discussed, with special reference to the addition of osmium tetroxide to the 3 : 4-bond of alkyl derivatives of 1 : 2-benzanthracene and 1 : 2-benzacridine.

IT has often been assumed that the reactivity of a double bond as exemplified by the velocity of an addition reaction is directly related to its double-bond character, or bond order. However, Gold (*Trans. Faraday Soc.*, 1949, **45**, 191) has recently pointed out that as the order of a bond is essentially a "static" property, it cannot provide an index of "dynamic" double-bond

character. This is, of course, strictly true; but the present paper attempts to show that the error in making this assumption is, in suitable cases, not significant.

The double-bond character, or the order of a bond, has been variously defined (see for example, Pauling, Brockway, and Beach, *J. Amer. Chem. Soc.*, 1935, **57**, 2705; Penney, *Proc. Roy. Soc.*, 1937, *A*, **158**, 318; Coulson, *ibid.*, 1939, **169**, 413; Pullman, *Ann. Chim.*, 1947, **2**, 5; Daudel and Daudel, *J. Chem. Physics*, 1948, **16**, 639; Walsh, *Trans. Faraday Soc.*, 1946, **42**, 779) and although it is essentially a theoretical concept, its physical reality has been well established by a study of bond-length variations (*e.g.*, Wheland, "Theory of Resonance," John Wiley and Sons, New York; Robertson, *Acta Cryst.*, 1948, **1**, 101). On the other hand, although a general agreement between the results of the different methods has frequently been claimed (Coulson, Daudel, and Daudel, *Rev. Sci.*, 1947, **85**, 29; Buu-Hoï *et al.*, *ibid.*, p. 1041) all the methods are admittedly approximate, and in any particular series of bonds, wide variations in the relative magnitudes of the orders may be obtained by several methods.

This may be readily appreciated by a comparison of the orders obtained by different methods for a comparable bond in a series of closely related hydrocarbons. A suitable series would seem to be the C–C-bond in benzene (I), the 1 : 2-bond in naphthalene (II), and the 1 : 2-bond in anthracene (III). The calculated double-bond characters and bond orders for these three bonds are given in Table I. If the bond order as calculated by the molecular-orbital method is accepted as a satisfactory index of double-bond character, the relative magnitude in this series of bonds



(I.) (II.) (III.) (IV.) (V.) (VI.)

is: 1 : 2-bond of anthracene > 1 : 2-bond of naphthalene > C–C-bond of benzene. The same order of relative magnitude is obtained by Pauling's method involving resonance between all the possible Kekulé structures. If, however, one assumes that the total charge of π electrons on the bond and its terminal carbon atoms provides a satisfactory index of double-bond character (as was done by Pullman, *loc. cit.*), then the order of relative magnitude becomes: 1 : 2-bond of naphthalene > 1 : 2-bond of anthracene > C–C-bond of benzene. Again, if one accepts the bond order as determined by the method of Daudel and Daudel, the order of relative magnitude becomes: 1 : 2-bond of naphthalene > C–C-bond of benzene > 1 : 2-bond of anthracene. Similarly, a comparison of the relative magnitudes of the double-bond characters of the 9 : 10-bond in phenanthrene (IV), the 3 : 4-bond in 1 : 2-benzanthracene (V), and the 1 : 2-bond in 3 : 4-benzphenanthrene (VI) also reveals gross irregularities. The molecular-orbital method

TABLE I.

Comparison of double-bond characters and bond orders for a comparable bond in a series of closely related hydrocarbons.[a]

Compound.	Bond.	Double-bond characters and bond orders. Pauling (*a*).	Pullman (*b*) (Total charge π electrons).	Pullman–Daudel (*c*).	Coulson (*d*).
Benzene	—	1·50	1·073[e]	1·464	1·667
Naphthalene	1 : 2	1·67	1·274	1·527	1·725
Anthracene	1 : 2	1·75	1·259	1·452	1·738
Phenanthrene	9 : 10	1·80	1·291	1·446	1·775
1 : 2-Benzanthracene	3 : 4	1·86	1·283	1·440	1·783
3 : 4-Benzphenanthrene	1 : 2	1·71	1·293	1·442	1·762

[a] Double-bond character by summation of Kekulé structures (Pauling, "Nature of the Chemical Bond," Cornell University Press, 2nd edn., 1940). [b] Total charge of π electrons. Sum of the "charge de liaison" and the two "indices de valence libre" (Pullman, *Ann. Chim.*, 1947, **2**, 5). [c] Bond order, by the valence-bond method (Pullman, *Ann. Chim.*, 1947, **2**, 5; Daudel and Daudel, *J. Chem. Physics*, 1948, **16**, 639). [d] Bond order by the molecular-orbital method (Coulson and Longuet-Higgins, *Rev. Sci.*, 1947, **85**, 929; Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, 1948, **226**, 1906).

[e] The various definitions of bond order, double-bond character, etc., are all basically different, and it is not to be expected that the different methods will give numerically equal values for any given bond. It is reasonable to expect, however, that all the methods will agree whether a given bond "A" is more like a double bond than another bond "B", or *vice versa*. As all the various methods are based on different approximations, this is not always the case, as the table indicates. The exact definitions and the approximations used in the various methods are given in the references quoted.

places these three bonds in the series: 3 : 4-bond of benzanthracene > 9 : 10-bond of phenanthrene > 1 : 2-bond of benzphenanthrene. Pullman's total-charge method, on the other hand, places the series in the reverse order.

That there is, in most cases, a qualitative relation between double-bond character, or bond order, and the velocity of an addition reaction can hardly be doubted. It is well known, for example, that when electron-releasing groups are attached to, or in close proximity to the double bond, the reaction rate is increased, and when electron-attracting groups are present, the reaction is retarded (Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692; Böeseken and Stuurman, *Rec. Trav. chim.*, 1937, **56**, 1034; De la Mare, *Quarterly Reviews*, 1949, **3**, 126). It is noteworthy that the rate of addition of osmium tetroxide to the dinaphthylethylenes is also consistent with the view that the greater the double-bond character (or density of π electrons), the more rapid the reaction (Badger, *Nature*, 1950, **165**, 647; cf. Chalvet and Daudel, *Compt. rend.*, 1949, **229**, 54).

In discussing the addition of ozone to aromatic double bonds however, Kooyman and Ketelaar (*Rec. Trav. chim.*, 1946, **65**, 859) pointed out that before the addition can be completed, the bond in question has to be converted into a "pure" double bond. More precisely, two π electrons have to be "localised." The initial degree of localisation is of great importance, as is evident from the fact that ozone always adds first to the bond having the greatest double-bond character, but it is conceivable that the polarisability will also be of significance, and that in certain cases it is of pre-eminent importance. This may be illustrated by reference to ethylene and its phenyl derivatives, for, as is well known, the phenyl group can act as an electron-donor or as an electron-acceptor, depending on the conditions. The rates of addition of halogens to ethylene and its phenyl derivatives decrease in the order, styrene > ethylene > stilbene, although the bond orders of the reactive bonds decrease in the order ethylene > styrene > stilbene. Furthermore, the rate of oxidation with peracetic acid decreases in the order styrene > stilbene > ethylene (Swern, *loc. cit.*; De la Mare, *loc. cit.*; Buu-Hoï *et al.*, *loc. cit.*).

Waters (*J.*, 1948, 727; see also Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900) has maintained that the correct method of assessing the reactivity at the various positions of an aromatic molecule is to estimate the energy difference between the normal state and the "quinonoid" transition state, and not merely to evaluate local electron densities. He points out that the oxidation–reduction potentials of the corresponding quinones can be used as indices of this energy difference, and it would seem therefore that the problem of the relationship between bond order and the "reactivity" may be approached indirectly through the oxidation–reduction potentials of the corresponding *o*-quinones. Indeed, following a study of the oxidation–reduction potentials of a number of *o*- and *p*-quinones derived from polycyclic aromatic hydrocarbons, Clar (*Ber.*, 1940, **73**, 104; "Aromatische Kohlenwasserstoffe," Berlin, 1941) pointed out that the quinones corresponding to the very reactive hydrocarbons have very little reactivity, and *vice versa*. The series: benzene, naphthalene, anthracene, naphthacene, and pentacene, is characterised by a very marked and progressive increase in "reactivity" and in the tendency to undergo addition rather than substitution reactions as the number of aromatic rings increases. The series of *p*-quinones: *p*-benzoquinone, α-naphthaquinone, anthraquinone, naphthacenequinone, and pentacenequinone, on the other hand, is characterised by an equally marked and progressive *decrease* in reactivity as the series is ascended. *p*-Benzoquinone has a potential of 0·71 volt, α-naphthaquinone of 0·48 volt, and anthraquinone, of 0·15 volt. Naphthacenequinone is less reactive still. It forms a vat (*i.e.* an alkaline solution of the quinol) only with difficulty, whilst pentacenequinone does not form a vat.

Some years previously, Fieser and Price (*J. Amer. Chem. Soc.*, 1936, **58**, 1838) called attention to the very great similarity between the addition of bromine to the 9 : 10-bond of phenanthrene, and the oxidation of phenanthraquinol. The substituents in the 2- and the 3-position of phenanthrene which were found to decrease the free energy of bromine addition (retard the reaction) are precisely those which were earlier (Fieser and Fieser, *J. Amer. Chem. Soc.*, 1935, **57**, 491) found to decrease the free energy of oxidation of quinols (increase the potential). Similarly, the substituents which increased the free energy of bromine addition also increased the free energy of oxidation of quinols. The free-energy change in the bromine addition was found to be much less than that in the oxidation, but Fieser and Price found that a given substituent has nearly the same *proportionate* influence in each case. It may be concluded, therefore, that there is a reasonably good correlation between the velocity of an addition to a suitable aromatic double bond, and the magnitude of the oxidation–reduction potential of the corresponding quinone. Clar's treatment, for example, predicts the 3 : 4-bond of 1 : 2-benz-

anthracene (V) to be more " reactive " than the 9 : 10-bond of phenanthrene (IV), and this has been confirmed experimentally for the addition of osmium tetroxide (Badger and Reed, *Nature*, 1948, **161**, 238). That there is a similar correlation between bond order and the oxidation–reduction potential of the corresponding *o*-quinone does not seem to have been noted previously. In Fig. 1 the bond orders of a series of aromatic bonds, as determined by the molecular-orbital method (Coulson and Longuet-Higgins, *Rev. Sci.*, 1947, **85**, 3280; Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, 1948, **226**, 1906; Baldock, Berthier, and Pullman, *ibid.*, 1949, **228**, 931) are plotted against the " corrected " oxidation–reduction potentials (Branch and Calvin, " The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, 1941) of the corresponding *o*-quinones. The distribution of the points indicates a very satisfactory degree of correlation between bond order and oxidation–reduction potential. It may also be reported that there is a fair degree of correlation between the oxidation–reduction potentials of a series of *p*-quinones and the sum of the two indices of free-valence (molecular-orbital method) for the corresponding positions in the related hydrocarbons.

FIG. 1.

Relationship between bond order (molecular-orbital method) and corrected oxidation–reduction potential of the corresponding o-quinone.

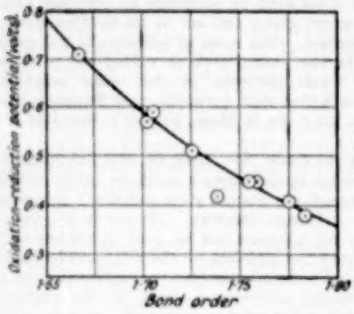


FIG. 2.

Ultra-violet absorption spectra, in alcohol.

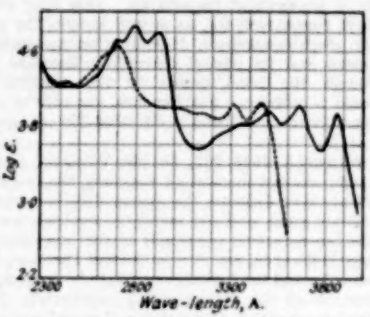


FIG. 2. ——— 5 : 7-*Dimethyl*-1 : 2-*benzacridine*. *Maxima at* 2440 (*log* ε 4·26), 2710 (4·71), 2790 (4·85), 2910 (4·80), 3400 (3·94), 3660 (4·01), 3880 (3·95).

– – – – – – 3 : 4-*Dihydroxy*-5 : 7-*dimethyl*-3 : 4-*dihydro*-1 : 2-*benzacridine*. *Maxima at* 2700 (4·67), 3150 (3·95) 3310 (4·02).

Osmium tetroxide is the most satisfactory reagent for the determination of the relative reactivity of aromatic double bonds, for it reacts only with double bonds and does not attack reactive *centres*, as do most other electrophilic reagents. This reagent has already been used (Badger, *J.*, 1949, 456) to study the relative reactivity of the 3 : 4-bond in a series of cancer-producing compounds related to 1 : 2-benzanthracene, and this series has now been extended by the inclusion of 3-methyl- and 9-methyl-1 : 2-benzanthracene. The rate of addition of osmium tetroxide to 5 : 7-dimethyl-1 : 2-benzacridine (VII) has also been determined. These alkyl benzanthracenes provide a series of closely related compounds in which there is, almost certainly, very little difference in polarisability. For this reason these compounds would seem to provide a suitable series for an examination of the degree of correlation between double-bond character and the velocity of an addition reaction.

Several attempts to assess the changes in double-bond character, or density of π electrons, with the introduction of methyl substituents into benzanthracene have now been published (Table II). In order to examine the relation between the double-bond character of the 3 : 4-bond of benzanthracene and its methyl derivatives, and their cancer-producing potency, Pullman (*loc. cit.*) calculated the total charge of π electrons on this bond for an extensive series of derivatives. The method was admittedly very approximate, but in spite of this there is a remarkably good agreement between the rate of addition and the total charge. The only serious discrepancy is with 9-methyl-1 : 2-benzanthracene, which reacts more rapidly than expected. Daudel and Martin (see Daudel, *Bull. du Cancer*, 1948, **35**, 110) attempted to apply the valence-

TABLE II.

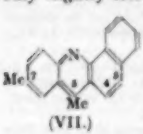
Comparison of the velocities of addition of osmium tetroxide to the 3 : 4-bond of substituted benzanthracenes with calculated double-bond characters.

Substituted 1 : 2-benzanthracene.	Rate constant (a), 10^2k_2.	Total-charge π electrons (b).	Free-valence numbers (c). $C_{(3)}$	$C_{(4)}$	Bond order (c).	Excess of charge on $C_{(3)}$ and $C_{(4)}$ (d).
1 : 2-Benzanthracene	0·48	1·283[a]	0·204	0·199	1·441	0
3-Methyl-	0·50	1·298	—	—	—	—
6-Methyl-	0·64	1·294	0·185	0·134	1·460	0·013
5 : 6-Dimethyl-	0·64	1·307	0·168	0·154	1·476	0·029
5 : 7-Dimethyl-	0·80	1·304	0·141	0·114	1·479	0·024
2′ : 7-Dimethyl-	0·83	—	—	—	—	0·035
10-Methyl-	0·91	1·306	0·177	0·167	1·436	0·027
9-Methyl-	0·96	1·296	1·187	0·172	1·456	0·016
9 : 10-Dimethyl-	2·7	1·319	0·160	0·139	1·459	0·043
5 : 6 : 9 : 10-Tetramethyl-	2·9	1·343	—	—	—	0·072

[a] See also Badger, *J.*, 1949, 456. [b] Pullman, *Ann. Chim.*, 1947, **2**, 5. [c] Dr. R. Daudel, private communication; see also Daudel, *Bull. du Cancer*, 1948, **35**, 110. [d] Daudel, *ibid.*, p. 110.

bond method rather more rigorously, and evaluated the bond orders and indices of free valence for a few selected compounds. Unfortunately, the valence-bond method seldom gives satisfactory results with substituted compounds, or with heterocyclic compounds, and several of the figures obtained would seem to be entirely unreasonable. For example, the calculated charge on the 3 : 4-bond of 1 : 2-benzanthracene was found to be *decreased* by the substitution of a methyl group in the 10-position. Indeed, in assessing the degree of correlation between these latter figures and the carcinogenic activity, Daudel was forced to conclude: " Il semble donc que l'accord entre la théorie et l'expérience soit moins bon dans le cas où l'évaluation des charges est plus correcte." However, by an alternative method, Daudel (*Bull. du Cancer*, 1948, **35**, 110; see also Daudel and Martin, *Bull. Soc. chim.*, 1948, **15**, 559) determined the " excess of charge " on the 3 : 4-positions produced by methyl substituents, or by the introduction of an annular nitrogen atom, as in the benzacridines. This treatment would seem to give a reasonable indication of the increase in double-bond character produced by a methyl substituent, and there is a fair degree of correlation between the rate of addition of osmium tetroxide and the magnitude of the " excess of charge." The case of 3-methyl-1 : 2-benzanthracene is interesting as the rate of addition is almost the same as with 1 : 2-benzanthracene itself. It seems likely that steric hindrance is a factor here. The rate of addition of osmium tetroxide to 9-methyl-1 : 2-benzanthracene was found to be comparable with that to the 10-methyl derivative, and more rapid than could be predicted by the " excess of charge." As was pointed out by Pullman (*Compt. rend.*, 1947, **224**, 1354) methyl groups in the *meso*-positions of this hydrocarbon are conjugated with the ring system to a much greater extent than methyl groups in other positions, and their effect on the 3 : 4-bond is therefore proportionately greater.

It is also noteworthy that osmium tetroxide adds to 5 : 7-dimethyl-1 : 2-benzacridine (VII) only slightly less rapidly than to the closely related 10-methyl-1 : 2-benzanthracene, and the degree of correlation between the velocity of the addition, and the " excess of charge " is, in this case, quite good.



(VII.)

The structure of the diols obtained by hydrolysis of the complexes of osmium tetroxide with various benzanthracenes has already been determined (Cook and Schoental, *J.*, 1948, 170; Badger, *J.*, 1949, 456, 2497). Hydrolysis of the complex with 5 : 7-dimethyl-1 : 2-benzacridine gave 3 : 4-dihydroxy-5 : 7-dimethyl-3 : 4-dihydro-1 : 2-benzacridine. The structure of this diol is confirmed by its ultra-violet absorption spectrum, which is similar to that expected for a derivative of phenyldimethylquinoline (Fig. 2). The ultra-violet absorption spectrum of 5 : 7-dimethyl-1 : 2-benzacridine, on the other hand, resembles that of 1 : 2-benzanthracene.

EXPERIMENTAL.

Reaction Rates.—Determinations of the rates of reaction with osmium tetroxide were carried out as previously described (Badger, *loc. cit.*).

3 : 4-Dihydroxy-5 : 7-dimethyl-3 : 4-dihydro-1 : 2-benzacridine.—Hydrolysis of the osmium tetroxide 5 : 7-dimethyl-1 : 2-benzacridine complex by Cook and Schoental's method (*loc. cit.*) gave *3 : 4-dihydroxy-5 : 7-dimethyl-3 : 4-dihydro-1 : 2-benzacridine* as beautiful colourless needles (from alcohol), m. p. 244°

after sintering and darkening (Found: C, 78·6; H, 5·6. $C_{19}H_{11}O_2N$ requires C, 78·3; H, 5·9%). The ultra-violet absorption spectrum (Fig. 2) was determined with a Beckman DU spectrophotometer.

I am indebted to Dr. Ng.Ph. Buu-Hoï for a gift of 5:7-dimethyl-1:2-benzacridine, and to Mr. R. S. Pearce for the absorption spectra. Microanalyses were carried out by Mr. R. Howard.

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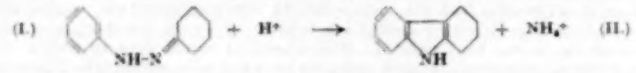
365. *The Fischer Indole Synthesis. Part IV. A Kinetic Investigation.*

By K. H. PAUSACKER and (the late) C. I. SCHUBERT.

The cyclisation of a number of phenylhydrazones of *cyclo*hexanone has been followed kinetically by determining the amount of ammonia liberated during the reaction. The reaction has been found to be of the first order when carried out in an excess of glacial acetic acid and of the second order when aqueous dioxan–sulphuric acid is used. The rates for seven hydrazones in glacial acetic acid under identical conditions are compared, and a theory is advanced for the mechanism of the reaction.

ALTHOUGH many theories have been advanced for the mechanism of the Fischer indole synthesis (cf. Robinson and Robinson, *J.*, **1918**, **113**, 639; **1924**, **125**, 827; Allen and Wilson, *J. Amer. Chem. Soc.*, **1943**, **65**, 611; Carlin and Fisher, *ibid.*, **1948**, **70**, 3421; Pausacker and Schubert, *J.*, **1949**, 1384), there is no published account of a kinetic investigation of this reaction.

If the reaction of the phenylhydrazone (I) of *cyclo*hexanone be considered, it is seen that, besides the formation of tetrahydrocarbazole (II), one mole of an ammonium salt is formed simultaneously. It was found that this reaction could be followed quite easily when glacial



acetic acid or aqueous dioxan–sulphuric acid was used as a solvent. At definite time-intervals, an aliquot was poured into a large excess of water, in order to "freeze" the reaction, and the organic matter was extracted with ether. The ammonium ion formed was then determined in a standard micro-Kjeldahl apparatus.

EXPERIMENTAL.

Reagents.—AnalaR glacial acetic acid was refluxed (1 hour) with 1% (by wt.) of chromium trioxide and distilled in an all-glass apparatus protected from moisture. Redistillation gave a constant-boiling fraction, free from ammonium ions.

Dioxan was purified by refluxing it over sodium and distilling the product twice.

The various hydrazones of *cyclo*hexanone were prepared by condensing the hydrazine with *cyclo*hexanone and purified by crystallisation from an appropriate solvent immediately before use. Their m. p.s agreed with those in the literature. *cycloHexanone* m-*methoxyphenylhydrazone* could not be crystallised and was a viscous liquid, b. p. 165—167°/0·8 mm. (Found: N, 13·2. $C_{13}H_{17}ON_2$ requires N, 12·8%). This distilled hydrazone did not contain any free ammonia or ammonium ion.

Methods.—(a) *Glacial acetic acid as solvent.* A weighed amount of the pure phenylhydrazone (*ca.* 1 g.) was placed in a 10-ml. standard flask immersed in the constant-temperature bath. After about 15 minutes, pre-heated glacial acetic acid was added with shaking, to make the volume up to the mark. After a further 5 minutes, the first aliquot was analysed, this being taken as zero time.

At definite intervals, 1-ml. aliquots were withdrawn (by means of a standard pipette kept in a tube immersed in the bath) and run into cold water (10 ml.) contained in a separatory funnel. The aliquot was extracted with ether (10 ml.), and the ethereal extract washed (twice) with water (5 ml.). The two combined aqueous solutions were placed in a micro-Kjeldahl apparatus, and sodium hydroxide solution (4 ml., 30%) added. The ammonia liberated was distilled into 10 ml. of 0·05*N*-hydrochloric acid. About 50 ml. of distillate were collected. The excess of hydrochloric acid was determined with 0·05*N*-sodium hydroxide, methyl-red being used as indicator.

(b) *Dilute sulphuric acid as solvent.* *cyclo*Hexanone phenylhydrazone (*ca.* 2 g.) was weighed into a 50-ml. standard flask immersed in the constant-temperature bath and dioxan–water (*ca.* 15 ml.; 7 : 3) was added. After *ca.* 15 minutes, concentrated sulphuric acid (1 ml.) was added with shaking, and the mixture made up to the mark with pre-heated dioxan–water. Aliquots (5 ml.) were withdrawn at determined times and run into cold water (10 ml.). This solution was then extracted with ether (25 ml.) and the ethereal extract washed twice with 5-ml. portions of water. Ammonium ion was determined in the usual manner.

Results.—(a) *Glacial acetic acid as cyclising agent.* The results of a typical run were :

Wt. of *cyclo*hexanone phenylhydrazone = 0·9999 g. = 10·65 ml. 0·0508N-HCl per aliquot.
x = ammonia formed, expressed in terms of ml. of 0·0508N-HCl.
Temp. = 44·70° ± 0·06°. $k_1 = \frac{2{\cdot}303}{t} \log_{10} \frac{a - 0{\cdot}84}{a - x}$ (sec.$^{-1}$).

t (sec.)	0	3558	6276	9960	14,574	19,866
x	0·84	2·72	3·92	5·38	6·64	7·75
$k_1 \times 10^4$	—	6·08	6·02	6·23	6·13	6·13

The results obtained by investigating the cyclisation of various hydrazones of *cyclo*hexanone in glacial acetic acid are shown in tabular form below. In each case, the value cited is the mean of the values obtained in two or more runs. The k_1 values all appear to be accurate within 2%.

R·NH·N:C$_6$H$_{10}$, R =	k(× 10^4) (44·7°).	k(× 10^4) (24·9°).	A.	E, kcals.*
p-NO$_2$·C$_6$H$_4$	Too slow to measure (1% reaction after 45 hrs. at 44·7°)			
m-MeO·C$_6$H$_4$	5·10 ± 0·07	0·744 ± 0·04	2·0 × 10^8	18·3
Ph †	6·18 ± 0·10	1·03 ± 0·02	3·2 × 10^9	17·0
β-C$_{10}$H$_7$	46·3 ± 0·8	8·36 ± 0·04	9·3 × 10^9	16·3
p-C$_6$H$_4$Me	47·0 ± 0·3	6·76 ± 0·10	2·3 × 10^9	18·5
α-C$_{10}$H$_7$	177 ± 3	29·4 ± 0·3	9·7 × 10^9	17·1
p-MeO·C$_{10}$H$_7$	Too fast to measure (97% reaction after 2 mins. at 44·7°).			
Ph	7·68 ± 0·13	[1·96% (by wt.) of water added]		
,,	9·37 ± 0·18	[5·33% (by wt.) of water added]		
,,	3·42 ± 0·03	(at 39·2°)		
,,	3·55 ± 0·02	(at 39·2°) [0·07% (by wt.) of quinol added]		

* The E values are accurate at least to 0·4 kcal.

† The same result was obtained when the initial weight of the phenylhydrazone was approximately doubled.

(b) *Sulphuric acid–dioxan–water as cyclising agent.* Only the phenylhydrazone of *cyclo*hexanone was investigated under these conditions. When approx. 1·5—1·6 moles of sulphuric acid per mole of the hydrazone were used, the reaction was of the second order.

t.	k_2 (mole l.$^{-1}$ sec.$^{-1}$).	
39·2° ± 0·06°	1·75 (± 0·03) × 10^{-4}	Frequency factor = 3·5 × 10^{11}
44·7° ± 0·06°	3·48 (± 0·07) × 10^{-4}	E = 24·7 kcals.

It was found that, when only 0·5 mole of sulphuric acid (*i.e.*, one equiv.) per mole of hydrazone was employed, the reaction stopped when 50% of the hydrazone had been used. This indicates that the ammonium hydrogen sulphate thus formed is not an effective catalyst.

In one experiment, the reaction was allowed to continue for 50 hours in order to ensure completion. A 92% yield of tetrahydrocarbazole (m. p. and mixed m. p., 118°) was isolated after addition of excess of water to the solution. An ammonium-ion determination indicated 96% conversion.

Discussion.

The rate of the reaction is evidently dependent on the availability of (solvated) protons in the reaction mixture, as it is seen that the "k" value increases from 6·18 × 10^{-4} in glacial acetic acid to 7·68 × 10^{-4} and 9·37 × 10^{-4} when 6·3 and 16·0 moles % of water are added. As the rate is dependent both on the concentration of hydrazone and on the acid concentration when sulphuric acid–dioxan–water is used, it is evident that the rate-determining step is the reaction between the original, or rearranged, hydrazone and a solvated proton.

Further evidence of the nature of the mechanism cannot be obtained as the values of E and A are too close to each other to allow any valid interpretation. In addition, it is found that Hammett's equation is not applicable.

With regard to the criticisms of our mechanism by Gore, Hughes, and Ritchie (*Nature*, 1949, **164**, 835), the following facts may be noted. In their examination of the reaction

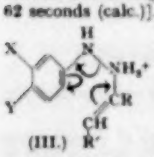
$$\underset{\text{(II.)}}{\text{A—NH—N=B}} + \text{C—NH—N=D} \longrightarrow \text{Tetrahydrocarbazole} + \text{products}$$

or R_2CO

or Ph·NH·NH$_2$

(II) is always a hydrazone which will not cyclise, and so the equilibrium of hydrazones will naturally be displaced in favour of that reactant which is removed from the system, *i.e.*, by cyclisation to form tetrahydrocarbazole. Although this work shows that hydrazone exchange may explain our mixed cyclisation results [as we have already stated (*J.*, 1949, 1386)], it does not, unfortunately, decide the crucial point, namely, whether or not, in our mixed cyclisations, cyclisation proceeds sufficiently slowly to allow exchange to be appreciable. This can only be settled by a determination of the relative rates of these two reactions. Gore *et al.* have also

drawn attention to the fact that 1 : 8-dimethylcarbazole is not among the products obtained by dehydrogenating the neutral fraction from the mixed cyclisation, but this point has already been discussed (*ibid.*, p. 1386). Finally, they assume that free radicals are not involved as during the cyclisation of *cyclo*hexanone phenylhydrazone in glacial acetic acid they (*a*) obtained a 95% yield, (*b*) did not isolate benzidine (from the dimerisation of $Ph\cdot NH^{\bullet}$) and (*c*) observed the evolution of only a small amount of carbon dioxide which they expected to be formed in large quantities by interaction of free radicals with the solvent. Although their generalised comments apply to certain free-radical reactions, the following observations may be pertinent. (i) Kharasch and Mayo (*J. Amer. Chem. Soc.*, **1933**, **55**, 2468) have found that the peroxide-catalysed addition of hydrogen bromide to allyl bromide gives a 92% yield of 1 : 3-dibromopropane. (ii) Wieland, Popper, and Seefried (*Ber.*, **1922**, **55**, 1816) were unable to isolate any diphenyl from the decomposition of phenylazotriphenylmethane even though free phenyl radicals are involved. (iii) The amount of interaction of these free radicals with the solvent cannot be determined and it is possible that the carbon dioxide observed by the above authors does arise from this source, and not from "a side reaction of unknown nature," particularly if it be assumed that the radicals formed have a high affinity for each other and relatively little affinity for solvent molecules. Their observation that the rapid evolution of carbon dioxide occurs as the mixture reaches the boiling point may be explained by the short duration of the reaction [$t_{\frac{1}{2}}$ (120°) = 62 seconds (calc.)]. Finally, although this reaction is indeed exothermic, it would possibly be incorrect to describe it as "strongly exothermic," and in solution one would not expect isolated points of high energy content sufficient to cause thermal decomposition of acetic acid as such phenomena are generally only noted in the gas phase at low pressure.



(III.)

With regard to the proposal by Calvin and Fisher (*J. Amer. Chem. Soc.*, **1948**, **70**, 3421), it may be noted that a methoxyl group in position X (of III) would be expected to facilitate reaction, whereas in position Y it would retard reaction. This is not in accord with our results, as we found that *cyclo*hexanone *p*-methoxyphenylhydrazone cyclises immeasurably more rapidly than the *m*-methoxy-compound.

The authors thank Mr. A. N. Hambly for much helpful discussion.

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CHEMISTRY DEPARTMENT, UNIVERSITY OF MELBOURNE. [*Received, February 23rd*, 1950.]

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366. 4-*Benzoyl*mesobenzanthrone.

By (the late) H. GORDON RULE, NEIL CAMPBELL, A. G. MCGREGOR, and A. A. WOODHAM.

Oxidative hydrolysis of 4-cyanobenzyl*meso*benzanthrone, readily obtained by the condensation of *meso*benzanthrone with benzyl cyanide, affords an excellent method for the preparation of 4-benzoyl*meso*benzanthrone. The constitutions of these products have been rigidly established.

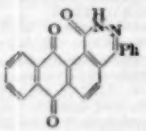
IN the presence of alkaline agents *meso*benzanthrone condenses with benzyl cyanide to give 4-α-cyanobenzyl*meso*benzanthrone [II; R = $Ph\cdot CH(CN)\cdot$]. Many such compounds on hydrolysis with caustic alkali yield the corresponding alkyl- or aryl-*meso*benzanthrone. We have found, however, that, although the above cyano-compound with acid hydrolysing agents gives 4-benzyl*meso*benzanthrone (II; R = $Ph\cdot CH_2\cdot$), with alkaline reagents in the presence of air it gives 4-benzoyl*meso*benzanthrone (II; R = $Ph\cdot CO$). After our work was completed we discovered that the preparation of 4-benzoyl*meso*benzanthrone by essentially the same method had been outlined in a German patent (G.P. 568,783). The benzoyl compound is also obtained by oxidative hydrolysis of the cyano-compound with acids and an oxidising agent, but the yields are poor. It was previously prepared by the oxidation of the benzyl compound with selenious acid (Kacer, G.P. 557,249).

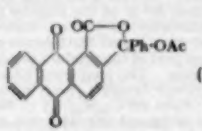
Presumably in such oxidative condensations the intermediate cyano-compound is hydrolysed to the carboxylic acid with simultaneous oxidation by the air. A parallel instance is furnished by sodium fluorene-9-carboxylate which undergoes oxidation and decarboxylation in alkaline solution to yield fluorenone (Wislicenus and Ruthing, *Ber.*, 1913, **46**, 2771).

How far other substances undergo nucleophilic attack by benzyl cyanide in alkaline solution is an interesting speculation but it is noteworthy that the product obtained from benzyl cyanide and *m*-dinitrobenzene (Reissert, *Ber.*, 1904, **37**, 831) may well be 1 : 3-dinitro-2- or -4-α-cyanobenzylbenzene (cf. Lobry de Bruyn, *Rec. Trav. chim.* 1889, **2**, 210). In agreement with this are the analytical figures of what was admittedly an impure product (Found : C, 60·7; H, 4·0; N, 14·8. Calc. for $C_{14}H_9O_4N_3$: C, 59·4; H, 3·2; N, 14·8%).

Evidence that oxidative condensation of *meso*benzanthrone in the presence of alkali occurs at the 4-position is to be found in the patent literature. It is, however, difficult to assess the reliability of such evidence, conclusive though it appears. This is due partly to the omission, in the patents, of relevant details such as the constitution or origin of important intermediates as well as lack of methods of identification or analytical figures, and partly to the comparative inaccessibility of the patent literature to academic workers. It was therefore decided to determine unequivocally the structures of the *meso*benzanthrone derivatives prepared above. This was done by synthesis and oxidation.

1-Bromo-4-methylnaphthalene (Meyer and Sieglitz, *Ber.*, 1922, **55**, 1839) was converted into 1-bromo-4-benzoylnaphthalene, identical with the product obtained from 1-bromonaphthalene and benzoyl chloride by the Friedel–Crafts reaction. Replacement of the bromine by the cyano-group gave 4-benzoyl-1-naphthonitrile (I) (B.P. 293,768), which was cyclised to 4-cyano-*meso*benzanthrone (II; R = CN) when heated with aluminium chloride and sodium chloride in a current of oxygen. Hydrolysis gave the 4-carboxylic acid (cf. Copp and Simonsen, *J.*, 1942, 209) which was converted into 4-benzoyl*meso*benzanthrone (II; R = COPh) identical with our compound prepared above by the oxidative hydrolysis of 4-α-cyanobenzyl*meso*benzanthrone. Any possibility that rearrangement had occurred during the ring-closure was eliminated by a second proof of the structure of 4-benzoyl*meso*benzanthrone. Oxidation gave 2-benzoylanthraquinone-1-carboxylic acid previously obtained from 1-chloro-2-benzoylanthraquinone (Scholl *et al.*, *Ber.*, 1936, **69**, 2428). The carboxyl group is in the 1-position and the benzoyl group must be contiguous to it since treatment with hydrazine hydrate or acetic anhydride in pyridine yielded a dihydropyridazine derivative (III) and an acetoxy-lactone (IV) respectively. Control experiments showed that hydrazine hydrate under the same conditions did not react with anthraquinone, and with anthraquinone-1-carboxylic acid gave the hydrazinium salt.

(III.) 

 (IV.)

Decarboxylation of 2-benzoylanthraquinone-1-carboxylic acid gave 2-benzoylanthraquinone, previously obtained from 9-benzoyl*meso*benzanthrone (Moshchinskaya, *Chem. Abstr.*, 1941, **35**, 5488) or anthraquinone-2-carboxylic acid (Waldmann *et al.*, *Ber.*, 1938, **71**, 370). It is of interest that, in contrast to anthraquinone-2-carboxylic acid and 1- and 2-naphthoic acids, 1-nitroanthraquinone-2-carboxylic acid and nitronaphthoic acids (cf. Rule *et al.* *J.*, 1934, 168, 171) are readily decarboxylated by copper in quinoline, thus further demonstrating the influence of negative substituents on decarboxylation.

Experimental.

Compounds denoted by asterisks are mentioned in patents but without analytical data.

Hydrolysis of 4-α-*Cyanobenzyl*mesobenzanthrone.—4-α-*Cyanobenzyl*mesobenzanthrone * was obtained by the method given in G.P. 501,082 (Friedländer, 1932, **17**, 1310) and separated from benzene in orange-yellow plates, m. p. 212° (Found : C, 87·4; H, 4·1; N, 4·1. $C_{31}H_{19}ON$ requires C, 87·0; H, 4·3; N, 4·1%). It (1 g.) was boiled for 7 hours with 75 c.c. of a mixture of glacial acetic acid, concentrated sulphuric acid, and water (4 : 2 : 1). Pouring the mixture into water gave a precipitate (0·9 g.) which after crystallisation first from benzene and then from glacial acetic acid gave 4-*benzyl*mesobenzanthrone as pale yellow needles, m. p. 182° (Found : C, 89·3; H, 5·2. $C_{31}H_{18}O$ requires C, 90·0; H, 5·0%). It gives an orange-red solution with a golden fluorescence when dissolved in concentrated sulphuric acid, but none with methanolic potassium hydroxide.

Oxidative Hydrolysis of 4-α-*Cyanobenzyl*mesobenzanthrone.—Similar treatment of 4-benzylcyano-

*meso*benzanthrone in presence of an oxidising agent such as potassium dichromate yielded only 4-benzyl-*meso*benzanthrone. In another experiment 4-cyano*benzylmeso*benzanthrone (1·5 g.), powdered sodium dichromate (4·5 g.), and glacial acetic acid (100 c.c.) were refluxed for 2—3 hours and then poured into water. The resulting solid was coagulated by heat and was washed with water, a brown resinous material resulting which was purified by dissolving it in benzene–light petroleum (11 : 9 parts), passing the solution through alumina, and developing the chromatogram first with a similar mixture and then with increasing proportions of benzene. A yellow band developed and passed into the filtrate which on evaporation yielded 4-*benzoylmesobenzanthrone*,* m. p. 175—177° (Kacer, *loc. cit.*, gives 174—176°) (0·3 g.) (Found : C, 86·3; H, 4·3. $C_{31}H_{16}O_3$ requires C, 86·2; H, 4·2%). It gives no colour with methanolic potassium hydroxide and gives a m. p. depression of 30° when mixed with 4-α-cyanobenzyl-*meso*benzanthrone. It is best prepared, however, by the method given in G.P. 568,783 (Friedländer, **1934**, **19**, 2127).

Synthesis of 4-*Benzoylmesobenzanthrone*.—1-Bromo-4-methylnaphthalene (Meyer and Sieglitz, *loc. cit.*) gave a 12% yield of 4-bromo-1-naphthoic acid, m. p. 211—212° (lit., 212°) when oxidised by dilute nitric acid. The acid (1 g.) was converted into the chloride by thionyl chloride (2 g.), and a benzene solution of the chloride was treated with aluminium chloride (1 g.), and the solution heated on the water-bath for 3½ hours. The mixture was poured into water, ice, and hydrochloric acid and thoroughly extracted with benzene. The benzene solution was chromatographed on alumina and developed with benzene–light petroleum (b. p. 60—80°). Elution of the dark zone at the top of the column with ethanol gave 4-*bromo*-1-*benzoylnaphthalene*,* which after repeated crystallisation from ethanol had m. p. 77° and gave m. p. 81—83° when mixed with the compound prepared as follows. 1-Bromonaphthalene (21 g.) was added to benzoyl chloride (14 g.) and aluminium chloride (14 g.) in carbon disulphide (80 c.c.), and the mixture after 2 hours on the water-bath was poured on ice (250 g.). Ether-extraction followed by evaporation of the dried ($CaCl_2$) extract gave crude 4-bromo-1-benzoylnaphthalene (11 g.) which on crystallisation from ethanol gave prisms, m. p. 87—88° (Found : Br, 25·9. $C_{17}H_{11}OBr$ requires Br, 25·7%).

1-Bromo-4-benzoylnaphthalene (9 g.), cuprous cyanide (5·5 g.), and freshly distilled pyridine (15 c.c.) were boiled for 17 hours in an oil-bath (temp. 210—220°) and poured into concentrated aqueous ammonia (25 ml.) and water (25 ml.). Benzene (25 ml.) and ether (25 ml.) were added and the mixture was filtered. The benzene–ether layer was washed 4 times with dilute aqueous ammonia (25 ml.), twice with 6*N*-hydrochloric acid (25 ml.), twice with water (20 ml.), and finally twice with a saturated solution of sodium chloride. Removal of the solvent gave 4-*benzoyl*-1-*naphthonitrile*,* m. p. 67—69° (5 g., 66%) (Found : N, 5·2. $C_{18}H_{11}ON$ requires N, 5·4%). The nitrile (2 g.), aluminium chloride (16·5 g.), and sodium chloride (3·5 g.) were well ground together and heated in an oil-bath (bath-temp. 115—120°) for 24 hours and the product was decomposed with water. The tarry product was dissolved in glacial acetic acid, from which crystals, m. p. 65—70°, separated. These were dissolved in benzene and the solution was chromatographed on alumina and the column developed with benzene–light petroleum. A pale yellow band moved down the column and consisted of unchanged nitrile, m. p. 68—69°, and a thin dark zone at the top of the column on elution with ethanol gave a small quantity of 4-*cyanomesobenzanthrone*,* m. p. 234°. The nitrile is best prepared by passing oxygen through the above molten mixture maintained at 110—135° for 24 hours and pouring the product into water. Extraction with ether followed by evaporation of the ethereal layer gave the nitrile which, crystallised from glacial acetic acid, had m. p. 234° (0·8 g., 12%) (Found : N, 5·45. $C_{18}H_9ON$ requires N, 5·5%). From the crystallisation liquors 3·0 g. of the original nitrile, m. p. 74°, were obtained.

4-Cyano*meso*benzanthrone (0·2 g.), water (2 ml.), concentrated sulphuric acid (2 ml.), and glacial acetic acid (2 ml.) were boiled for 5 hours and then poured into water. Hydrolysis was found to be incomplete and that part of the product which was insoluble in aqueous sodium carbonate was hydrolysed for a further 9 hours. The combined alkaline extracts on acidification yielded *meso*benzanthrone-4-carboxylic acid, yellow crystals (from nitrobenzene), m. p. 314—315° (yield, quantitative) (Found : C, 78·5; H, 3·65. Calc. for $C_{18}H_{10}O_3$: C, 78·8; H, 3·65%). The acid chloride [prepared from the acid (0·2 g.) and excess of thionyl chloride], benzene (10 ml.), and aluminium chloride (0·5 g.) were boiled for 4 hours and poured into concentrated hydrochloric acid and ice. The benzene layer was removed and the aqueous layer extracted 3 times with benzene. The combined benzene extracts, after drying (Na_2SO_4), gave on concentration a brown solid, which was dissolved in benzene and passed through a column of alumina (3 × ½ in.). A yellow zone passed quickly down the column and gave a product which after crystallisation first from benzene and then from ethanol yielded yellow crystals of 4-benzoyl-*meso*benzanthrone, m. p. 176°, undepressed when mixed with the benzoyl compound prepared as above (Found : C, 85·7; H, 4·3%).

4-*Methyl*-1-*naphthonitrile*.—4-Bromo-1-methylnaphthalene (10 g.), cuprous cyanide (6 g.), and pyridine (10 c.c.) were heated for 18 hours in an oil-bath, the temperature of which was 215—225°. The product was worked up as for the nitrile described above and gave 4-*methyl*-1-*naphthonitrile*, needles (from light petroleum), b. p. 210—220°/40 mm., m. p. 53—54° (Found : N, 8·1. $C_{12}H_9N$ requires N, 8·4%). In view of the above successful synthesis, conversion of the nitrile into 4-benzoyl*meso*benzanthrone was not attempted.

Oxidation of 4-*Benzoylmesobenzanthrone*.—4-Benzoyl*meso*benzanthrone (0·5 g.), chromic anhydride (AnalaR; 1·5 g.), and glacial acetic acid (15 ml.) were boiled for ½ hour and poured into water (150 ml.). 2-Benzoylanthraquinone-1-carboxylic acid thus obtained was dissolved in sodium hydroxide solution, precipitated from the filtered solution by hydrochloric acid, and crystallised from benzene in needles, m. p. 212—216° (10%). A purer acid was obtained by reducing the volume of the above aqueous liquor, whereupon cooling gave the acid, m. p. 234° (lit., 224°) (33%) (Found : C, 72·9; H, 3·3. Calc. for $C_{22}H_{12}O_5$: C, 74·2; H, 3·3%).

The acid (0·2 g.) and 50% hydrazine hydrate (3·0 ml.) were heated for 30 minutes. The dried product (0·2 g.) was crystallised first from glacial acetic acid and then from ethanol to give yellowish crystals of 3-*keto*-6-*phenyl*-2 : 3-*dihydroanthraquinono*(1′ : 2′-4 : 5)*pyridazine*, m. p. 324—327° (Found : C, 73·7; H, 3·6; N, 7·4. $C_{22}H_{11}O_3N_2$ requires C, 74·9; H, 3·4; N, 8·0%). The substance was insoluble in

sodium carbonate solution and its ethanolic solutions had a pronounced olive-green fluorescence. *o*-(*p*-Toluoyl)benzoic acid similarly gave *3-keto-6-phenyl-2 : 3-dihydro-4 : 5-benzpyridazine*, colourless plates (from glacial acetic acid), m. p. 258—259°, insoluble in sodium carbonate solution (Found : N, 11·3. $C_{14}H_{11}ON_2$ requires N, 11·9%). Under similar conditions anthraquinone was unchanged by hydrazine hydrate and anthraquinone-1-carboxylic acid gave the *hydrazinium* salt, m. p. >380° (Found : N, 10·3. $C_{15}H_{12}O_4N_2$ requires N, 9·9%), which with hydrochloric acid regenerated the original acid.

2-Benzoylanthraquinone-1-carboxylic acid (0·1 g.), pyridine (0·7 ml.), and acetic anhydride (0·35 ml.) were heated on the steam-bath for 3 hours and poured into water. The *acetoxy-lactone* [*5'-acetoxy-5'-phenyl-2' : 5'-dihydrofuran-2'-one*(3' : 4'-1 : 2)*anthraquinone*] separated and crystallised from glacial acetic acid in pale yellow needles, m. p. 255—256° (Found : C, 71·8; H, 3·8. $C_{24}H_{14}O_4$ requires C, 72·4; H, 3·5%).

2-Benzoylanthraquinone-1-carboxylic acid on decarboxylation at 170° for ½ hour with quinoline and copper gave 2-benzoylanthraquinone, m. p. 216—217° (Found : C, 80·3; H, 3·6. Calc. for $C_{21}H_{12}O_3$: C, 80·7; H, 3·8%). Under similar conditions anthraquinone-1-carboxylic acid and 1-nitroanthraquinone-2-carboxylic acid gave anthraquinone and 1-nitroanthraquinone respectively, but anthraquinone-2-carboxylic acid and α- and β-naphthoic acids gave only unchanged acids.

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367. *Separation of the Lanthanons with the Aid of Ethylenediamine-NNN'N'-tetra-acetic Acid.*

By J. K. Marsh.

A preliminary survey of the possibility of separating the lanthanons by fractional precipitation of oxalates or other insoluble salts on breaking their complexes with ammonium or alkali salts of ethylenediaminetetra-acetic acid shows that valuable results are achieved. By this mode of fractionation, yttrium comes close to dysprosium in the lanthanon series, and is separated very rapidly from erbium and the ytterbium earths. A rapid separation of all the heaviest earths, which form the firmest complexes, is also indicated. The method is recommended as being superior to double alkali-sulphate precipitation for an initial separation.

The recent trend in the chemistry of the lanthanons has been to recognise the limitations of older fractionation processes for separating members of the group in purely cationic form, and to use less fully exploited physical processes such as solvent extraction, or chemical processes involving formation of more or less stable anionic complexes. In this way it has been found possible to utilize differences in the stability of complexes. The most notable example is the success achieved in the use of ammonium citrate and citric acid solution to form a complex with and elute the cations held in an ion-exchange resin such as " Dowex 50." As a micro-method this process is excellent, but the large quantities of reagents and water required detract seriously from its merits as a production process. Even many of the older classical fractionation processes are based upon weak complex formation, as found in the so-called double salts, *e.g.*, with alkali sulphates, ammonium oxalate, ammonium nitrate, and magnesium nitrate. The strong co-ordinating power of citrates and tartrates has long been known but was not successfully utilised until the advent of the ion-exchange technique. Strong complexes are formed by the " Komplexones " developed by Schwarzenbach and his school (*Helv. Chim. Acta*, 1945, **28**, *et seq.*), and Beck (*ibid.*, 1946, **29**, 357; *Mikrochem.*, 1947, **33**, 344; *Anal. Chim. Acta*, 1949, **3**, 41) has shown that ammonium and alkali salts of nitrilotriacetic acid, $N(CH_2{\cdot}CO_2H)_3$, " trilo," are very successful in effecting semimicro-scale separations. He dissolved the oxalates in weakly alkaline " trilo " solutions, and reprecipitated them by acidification, or addition of an uncomplexed lanthanon salt or cupric salt solution. This he called the " exchange method," since the copper or the more weakly basic lanthanons combined with the " trilo," displacing the stronger bases which were then precipitated as oxalate; for instance, from a 90% La_2O_3 preparation a 75% yield of pure La_2O_3 was obtained in one operation by acidifying the trilo-complexed oxalate solution with acetic acid.

Of the numerous substances of similar chemical constitution (*i.e.*, having one or more secondary or tertiary amino-groups, and two or more acetate radicals so disposed as to give rise to chelate structures), trilo and ethylenediaminetetra-acetic acid, $[{\cdot}CH_2{\cdot}N(CH_2{\cdot}CO_2H)_2]_2$, " H_4 enta," were the most powerful co-ordinating agents found by Schwarzenbach *et al.* for the alkaline earths until they recently prepared 1 : 2-diamino*cyclo*hexane-*NNN'N'*-tetra-acetic acid (*Helv. Chim. Acta*, 1949, **32**, 1682). They have derived a constant whereby the power of the

various substances can be compared for bivalent metals, by combining the acidity constants for the substance with the equilibrium constants for the reaction between metal ions and complex, yielding metal complex and hydrogen ions (*ibid.*, pp. 1543, 1682; *Nature*, 1949, **163**, 723). The values of the constant for calcium, log K_{Ca}, are for trilo, enta, and the 1 : 2-*cyclo*hexane compound, respectively, 6·41, 10·5, and 12·5. The bivalent elements, it is found, can be arranged in order of co-ordinating tendency irrespective of the agent used, with only minor exceptions. Similarly, the values of the complex-formation constants show that in general each agent has a characteristic degree of efficiency relative to the others; *e.g.*, it may be expected that enta will exceed trilo in the stability of its lanthanon complexes. However, when we change from a bivalent to a tervalent element, a new disturbing condition arises to upset any prediction, but it has been found that enta behaves similarly with bivalent metals and with lanthanum and cerium (*Helv. Chim. Acta*, 1948, **31**, 459). The ions H enta^{3-}, H_2 enta^{2-}, and H_3 enta^{1-} thus appear to build complexes with these two elements just as with bivalent elements, but aluminium, ferric iron, and chromium behaved differently and formed hydroxo-complexes, *e.g.*, [Al enta(OH)]$^{3-}$, or held a water molecule.

Since H_4 enta is manufactured in quantity for textile processing, it is freely available for separation of lanthanons. Its low solubility in cold water (0·03 g./100 g.; Bird, *J. Soc. Dyers Col.*, 1939, **55**, 560; **56**, 473) enables it to be recovered by acidification after use.

As a first step for the separation of a crude lanthanon mixture, the application of enta is found to be superior to the classical alkali double sulphate precipitation. The latter process has usually been limited to one or two applications only, owing, not to any inefficiency *per se*, but to the large amount of labour involved in decomposing the double sulphates with alkali and washing the hydroxides free from alkali. Introduction of silica by the alkali also causes much trouble. A partial solution of the difficulty is to roast the double sulphates till anhydrous (Marsh, *Nature*, 1949, **168**, 998). After being ground, all can be brought into solution easily with iced water provided that not too much terbium earths are present; or the yttrium earth solution may be decanted and the insoluble terbium earth residue centrifuged. The efficiency of a single double sodium sulphate precipitation of the crude earths from a quantity of Norwegian gadolinite can be seen from Table I. The precipitates of double sulphate were collected, and the derived oxides analysed spectrophotometrically as far as possible.

TABLE I.

Double sodium sulphate precipitates from crude (Ce-*free*) *gadolinite earths.*

Fraction no.	1	2	3	4	5	6	7	8	9
% of total	10	10	6	21	6	14	20	11	2
Apparent at. wt.	137	124	114	107	102	97	102	107	127
Oxides, % :									
Pr	6·3	2·5	0·8	—	—	—	—	—	—
Nd	32·4	12·3	3·6	—	—	—	—	—	—
Sm	24·8	12·2	6·2	2·4	—	—	—	—	—
Dy	—	10	13·8	11·0	8·3	6·2	3·9	1·0	—
Ho	—	1·7	2·0	2·1	1·9	1·7	1·6	0·8	0·1
Er	—	—	—	5·5	6·1	6·3	7·5	6·8	4·3
Yb	—	—	—	—	—	—	—	8·0	32·6

TABLE II.

Fractions 1 *and* 2 *of Table* I *refractionated with "enta."*

Fraction no.	1	2	3	4	5	6	7
% of total	22	12	28	17	10	7	4
Oxides, % :							
Pr	10·4	9·3	5·0	0·5	—	—	—
Nd	44·0	43·0	29·0	4·8	0·4	—	—
Sm	10·0	12·0	18·5	7·5	1·5	—	—
Dy	—	—	—	17·6	18·2	16·1	11·7
Ho	—	—	—	1·4	2·4	3·1	4·4
Er	—	—	—	—	4·0	7·3	20·0
Yb	—	—	—	—	—	0	10·0

The first two double sulphate fractions represented in Table I formed the starting material used to ascertain the separational effect brought about by enta, and represented in Table II. The two oxides were united and dissolved in nitric acid, and nine-tenths of the solution precipitated as oxalate. To this was added just sufficient ammonia and ammonium enta solution to cause all the oxalate to dissolve when hot to a solution smelling faintly of ammonia. The reserved

tenth part of nitrate solution was then run in while the oxalate solution was stirred mechanically at its boiling point. Thus there resulted fraction 1 of Table II, since the amount of enta was unable to co-ordinate with the whole of the lanthanon now present, and some material forming the least stable complexes (*viz.*, lanthanum and the cerium earths) was precipitated as oxalate. Subsequent precipitates 2, 3, 4, and 5 were formed by running 10% oxalic acid solution into the hot, stirred complex solution, but solid oxalic acid was used for fractions 6 and 7. The whole of the lanthanon was then seen to be precipitated, and the solution contained nearly 10% of oxalic acid. It was thus nearly saturated when cold. From it, much the greater part of the H_4 enta was recovered next day.

On comparing Tables I and II the following deductions can be made. (1) The concentration of neodymium is at least as effective by enta as by double sulphates. (2) Dysprosium collects by double sulphates in the early middle fractions, whereas by enta it is spread more evenly throughout the yttrium fractions: this is further exemplified in Table III*b*. Conversely, yttrium precipitated in presence of enta is collected at or close to the position of dysprosium in the lanthanon series, whereas by double sulphates it is collected just above the position of erbium, and a considerable Y–Dy separation results. (3) This leads also to the observation that erbium and ytterbium are collected much better in the tail fractions by enta than by double sulphates. It should be noted that Tables I and II represent the separation of the cerium and the yttrium group too sharply. Each group can only be determined satisfactorily in the absence of the other; *e.g.*, erbium cannot be assayed in presence of neodymium. Thus the erbium represented in Table II could not be determined in fractions 1 and 2 of Table I from which all of Table II is derived. Also estimates of samarium are made at a short wave-length and are apt to be high owing to traces of Ce(IV) or Fe(III), etc. This appears to have caused higher estimates in Table I than are found in Table II. The great advantage of enta, however, is not any superiority which it can give in one fractional precipitation, but the fact that it always yields oxalates which require little processing before again being fractionated. Thus the enta fractionation can be carried on continuously without the labour involved each time double sulphates have to be brought again into solution.

TABLE III.

		(*a*). Tb-free yttrium earths, %:					(*b*). Dy-rich yttrium earths, %:		
Fraction no.	%	Dy_2O_3.	Ho_2O_3.	Er_2O_3.	Yb_2O_3.	%	Dy_2O_3.	Ho_2O_3.	Er_2O_3.
1	16	1·5	·6	3·6	—	42	26·0	1·7	1·3
2	19	1·5	2·7	4·0	—	13	22·6	1·4	0·7
3	34	1·8	2·0	7·7	—	12	27·6	1·8	1·1
4	10	1·8	3·6	6·7	—	9	31·4	2·5	2·3
5	9	2·8	1·8	10·2	6·2	16	30·8	3·7	3·8
6	8	0·7	1·8	18·9	15·7	6	23·4	6·4	11·2
7	4	0·0	0·8	14·5	50·0	2	26·7	7·9	25·3

TABLE IV.

Input of mixed oxides: (*a*), Nd, 85% + Pr, 15%; (*b*), (*c*), (*d*), and (*e*), La, 12·5% + Pr, 87·5%.

Col. (*a*): NH_4 salt of "enta" Pr and Nd oxalates, and oxalic acid.
" (*b*): Na " " La " Pr " " Pr succinates, and Cu acetate.
" (*c*): Na " " La " Pr succinates, and Cu acetate.
" (*d*): K " " La " Pr " "
" (*e*): NH_4 double citrates of La and Pr, and oxalate ion.

	(*a*)		(*b*)		(*c*)		(*d*)		(*e*)	
Fraction.	%	Pr_6O_{11}, %	%	La_2O_3, %	%	La_2O_3, %	%	La_2O_3, %	%	La_2O_3, %
1	27	16·2	2	25	43	19·6	36	20·3	11	13·2
2	10	16·5	11	23	39	8·5	15	15·6	40	16·0
3	26	16·5	22	15·5	18	4·6	26	11·3	16	13·2
4	23	13·0	10	17	—	—	13	6·0	24	11·2
5	11	9·4	12	13	—	—	7	2·4	7	9·5
6	3	7·2	33	7	—	—	3	16·3 *	2	9·2
7	—	—	10	2·7	—	—	—	—	—	—

* A small final precipitate obtained by oxalic acid and obviously containing potassium oxalate.

Table III*a* shows the result of operating with a concentrated solution of crude yttrium oxide of apparent molecular weight of 250, which had been freed from terbium and earlier earths in the series, and partly fractionated as basic nitrates till considered too poor in coloured earths to repay further extraction. A similar run was done at ten times the dilution, and showed only a

slight improvement in separation. Thus erbia rose in fraction 6 from 19 to 23%, and ytterbia from 50 to 56%, and it was not found at all in fraction 5 of the dilute solution. The effect of dilution is thus of minor importance and is overridden by considerations of convenience. It should be noted that second and third quantities of yttrium nitrate solution together with ammonium oxalate were added to the original enta–oxalate solution, so that not much change in composition of fractions 1—3 of Table IIIa was to be expected. 0·4 Mol. of oxide (100 g.) was here processed in 600—800 ml., though not more than 40 g. were in solution at any one time. It appears that even more (0·6—0·8 mol.) might still have given satisfactory results.

Table III*b* shows the result of operating with a mixture rich in dysprosium. Very little change in dysprosium content relative to yttrium took place. Holmium, however, is seen more clearly than in Table IIIa to be collecting at the tail.

Table IV*a* presents praseodymium contents of fractions obtained by operating with a mixture 85% Nd_2O_3 + 15% Pr_6O_{11}. Further systematic fractionation would be required to enable an assessment of the utility of enta for separating these two oxides, but the prospect is not unfavourable. It may be noted that in Table II the Pr : Nd ratio is seen to change from 1 : 4 in fraction 1 to 1 : 6 in fraction 3.

Table IV *b*, *c*, *d*, and *e* illustrates the change in lanthanum content of fractions obtained under various conditions by precipitating the same mixture of Pr_6O_{11}, 87·5% + La_2O_3, 12·5%. Table IV*b* shows the outcome of using the sodium salt of enta on the oxalates. The ammonium salt was also used, but not all the fractions were analysed. The first and second small precipitates contained 14% and 18% of La_2O_3, respectively. At various times it has been found that poor separation was shown by the first precipitate. This is thought to have been due to working at too high a pH, with solutions containing metastable hydroxide. Values over 8·5 seem undesirable. Precipitates from basic solution were always fine or even unfilterable, though easily centrifuged. The last fraction from the ammonium salt (32%) contained 3·9% of La_2O_3. The amount of lanthanum therefore does not appear to be appreciably different from the content of the tail fractions from the sodium salt.

Table IV*c* and *d* shows the results of co-ordination of succinates with the sodium and potassium salts of enta respectively. The complexes were then broken by adding cupric acetate. The copper took the place of the lanthanon, which was precipitated as succinate. By this method little change in pH occurred during the fractionation.

Table IV*e* gives the effect of formation of a complex with ammonium citrate and then reprecipitation by addition of first ammonium oxalate and then oxalic acid. Large amounts of the latter were required before quantitative precipitation could be brought about. The separation achieved is seen to be much inferior to any of the enta series. Whereas these gave La_2O_3 between 25 and 3%, the citrate series varied only between 16 and 9%.

The effect of conditions on the degree of separation achieved by means of breaking the complex in enta solutions of the lanthanons appears to be small. Displacement of lanthanon by copper at constant pH in place of displacement of enta by oxalic acid by lowering the pH, or use of co-ordinated succinates in place of oxalates are all without any large effects upon the degree of separation brought about. Oxalate seems slightly superior, and its use is easier and cheaper.

It has been found that 1 mol. of enta will cause solution of 1 g.-atom of a lanthanon. The simple salts of lanthanon–enta are insoluble, and have the formula LnH (enta) (Brintzinger, Thiele, and Muller, *Z. anorg. Chem.*, 1943, **251**, 285), and it seems likely that the highly soluble alkali or ammonium oxalate complexes, which, however, may be obtained crystalline, must have a formula like that inset.

$(NH_4)_3\left[\mathrm{Ln}\begin{matrix}(\mathrm{enta})\\ C_2O_4\end{matrix}\right]$

The use of ethylenediaminetetra-acetic acid or future improved co-ordinating agents of similar type gives promise of effecting revolutionary simplification of the purification of the lanthanons, except dysprosium and those in the series near to it. The reagent appears to be most efficient for the four heaviest lanthanons, but it is likely to be of use also with the lightest.

Experimental.

Precipitation of Crude Gadolinite Earths (Table II).—The oxides used (Fractions 1 and 2 of Table I) varied in molecular weight from 318 to 292 and contained very little cerium. A stock ammonium enta solution was prepared by dissolving H_4 enta in sufficient ammonia to give $H_3(NH_4)_1$ enta equivalent to 250 g./l. of H_4 enta. 24 G. of oxalate were formed into a complex with sufficient of this solution (60 ml.) with added ammonia to give a clear solution at the b. p. To this was added a quantity of nitrate solution. The precipitation of the oxalates has already been described, and with slight modifications was in accordance with the procedure generally adopted in all the experiments here reported. The volume of solution was 500—700 ml., and the total oxide 10 g.

Separation of Yttrium Earths, and Determination of the Enta Requirement for Complex Formation (Table IIIa).—25 G. of impure yttrium oxide (*M*, 250; 0·10 mol.) were converted into oxalate. This required 250 ml. (0·214 mol.) of the above stock enta solution, thus demonstrating a 1 : 1 ratio between enta and lanthanon in the complex. The later oxalate precipitates were coarse and appeared to be mixtures.

The precipitation of H_4 enta even at the b. p. will occur when a lanthanon solution of good working concentration is progressively acidified with oxalic acid. Mixed precipitates of oxalate and H_4 enta, or possibly acid or normal lanthanon enta salts or mixed enta–oxalato-salts, are then encountered. When rich in oxalates, the precipitates may most conveniently be ignited, but when rich in enta, the whole of the lanthanon can be removed by boiling the precipitate with a quantity of water, filtering the solution hot, and allowing it to stand overnight. The lanthanon passes into solution at the b. p., but is precipitated as oxalate together with a little H_4 enta or its normal salt, etc., on cooling. The mother-liquor is again boiled with the H_4 enta, and the process repeated so long as lanthanon continues to be extracted. Two or three repetitions give a clean separation of lanthanon, and recovery in a pure state of the bulk of the enta at the lutecium end of the series. Since oxalic acid is sufficiently strong to displace H_4 enta, the final working solution when containing about 8% of oxalic acid at room temperature contains very little enta, and so has little co-ordinating power. The excess of oxalic acid ensures full precipitation of the lanthanon. This has been proved by evaporation to dryness, and ignition of the residue from 100 ml. of solution. No trace of lanthanon was found in it after working on a material rich in ytterbium and lutecium. The last traces of lanthanon oxalate, however, are precipitated only after several days, and may be contaminated with iron.

The Normal Lanthanon–Enta Salts.—Brintzinger *et al.* (*loc. cit.*) have found NdH enta and LaH enta to be insoluble or even highly insoluble salts. By direct union of the oxides of gadolinium and ytterbium and H_4 enta, the author has found that slightly soluble salts result. The solubility of the series appears to increase from lanthanum to lutecium. In an attempt to prepare the oxalate of ytterbium, an insoluble salt containing enta was obtained. However, on precipitation of sufficiently dilute ytterbium–enta solution pure oxalate was obtained. Enta salts will fuse and behave quite differently from oxalates when ignited. The possibility is being explored of fractionating the ytterbium group earths with little or no univalent metal present.

An ammonium–yttrium–enta salt has been prepared as short needles, but it is too soluble and sluggish in crystallisation to afford a means of fractionation.

Dysprosium Fraction (Table IIIb).—5 G. of oxide were used of which half was converted into a complex as oxalate and half then added as nitrate. The initial solution was very alkaline, and the poor separation obtained in the first fraction is believed to be due to this. The experiment was carried out as before with a final volume of about 400 ml.

Separation of Neodymium and Praseodymium (Table IVa).—The oxide used (10 g.) consisted of Nd_2O_3, 85% + Pr_6O_{11}, 15%. 7·5 G. of oxide were formed into a complex with oxalate, and 2·5 g. added as nitrate to a solution of pH 8·5. Subsequent additions of oxalic acid were made. The final precipitate was crystalline and appeared free from H_4 enta, yet on ignition it behaved differently from a pure oxalate, so it is possible that it was a double enta–oxalate salt.

Separation of Lanthanum and Praseodymium (Table IV*b*, *c*, and *d*).—Tests were made with both ammonium and sodium as univalent cation, but no pronounced difference resulted. Succinates were also tried, both sodium and potassium being used as cations. The precipitation by cupric acetate was apt to be delayed and then sudden. The pH was about 7 and the precipitates required to be centrifuged. When the pH was lowered, not all the succinate would precipitate. No advantages were gained by the use of succinates.

Separation of Citrate (Table IV*e*).—Ammonium citrate was added to a praseodymium nitrate solution, but only a partial precipitation occurred. Enough was then added again to clear the hot solution. Two precipitates were obtained by adding ammonium oxalate, but further precipitates were only obtainable by using oxalic acid.

The author thanks Sir Robert Robinson, O.M., P.R.S., for laboratory facilities, and the Government Grants Committee of the Royal Society, and Messrs. Johnson, Matthey & Co. Ltd. for financial assistance.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, March 6th*, 1950.]

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368. *Aromatic Hydrocarbons. Part LVIII. The Structure of Azulene.*

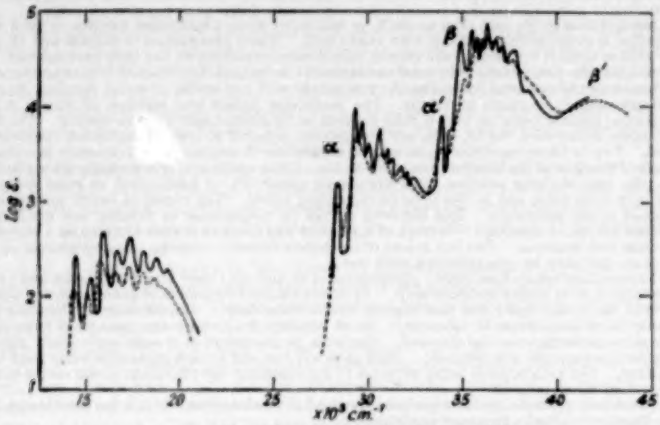
By E. CLAR.

Comparison of the visible and the ultra-violet absorption spectrum at room temperature and at −170° gives the characterisation and classification of the different band groups. The results thus obtained correlate the aromatic state of azulene with the ultra-violet part of the spectrum, whilst the visible part is correlated with a non-aromatic metastable state.

THE anellation principle provides a simple relation between the absorption spectrum and the number of π-electrons in an aromatic hydrocarbon (Clar, *Chem. Ber.*, 1949, **82**, 495). Thus the first group of bands (α-bands) in benzene at 2600 A. shows a steady shift to the red with increasing

number of π-electrons in passing to naphthalene, phenanthrene, and the higher phenes (angular aromatic hydrocarbons).

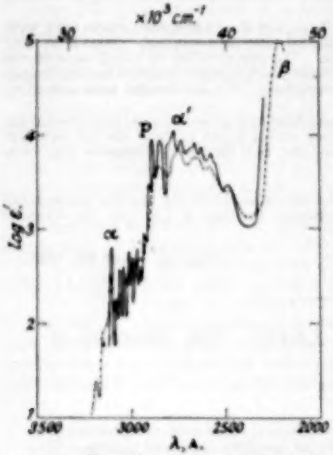
FIG. 1.



– – – – – *Absorption spectrum of azulene at* +18°.
——— " " " −170°.

This rule would require a similar group of α-bands for azulene and naphthalene. If allowance is made for the fact that the average angle in uniplanar azulene is greater than the 120° of the benzenoid hydrocarbons, a small shift might be expected. This is indeed the case. The first ultra-violet group of bands lies between that of naphthalene and phenanthrene. Investigation at low temperature has shown beyond any doubt that these are α-bands. This class of bands is characterised by a very small (or no) ultra-violet shift at low temperature. (For the classification of bands, see Clar, *J. Chem. Physics*, 1949, **17**, 741; *Spectrochim. Acta*, 1950, in the press.)

FIG. 2.



– – – – – *Absorption spectrum of naphthalene at* +18°.
——— *Absorption spectrum of naphthalene at* −170°.

There is another band of the α-type, marked α' in Fig. 1. This band corresponds to the α'-band in the absorption spectrum of naphthalene at −170°; it is superposed on a group of *p*-bands (Fig. 2). If the α-bands are the result of a resonating system of 10 π-electrons, the anellation principle would require 6 π-electrons for the α'-bands in naphthalene and azulene. This means that 4 π-electrons would be localised in each ring, whilst 2 π-electrons could move from one ring into the other. However, this idea requires the support of more experimental material, which is forthcoming in the higher acenes (linear aromatic hydrocarbons).

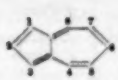
Owing to the non-benzenoid character of azulene no trace of a group of *para*-bands, corresponding to the group beginning in naphthalene at 2885 A., can be found in the spectrum of azulene. The anellation principle correlates the *p*-bands with the transition from the ground state to a Dewar or *para*-form in the excited state. These bands which become the most prominent in the higher acenes are

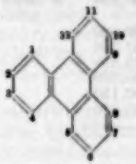
characterised by a red shift of about 300 cm.$^{-1}$ at low temperature (Clar, *Spectrochim. Acta*, 1950, in the press).

There is an extended group of β-bands in the spectrum of azulene between frequencies of 35,000 and 40,000 cm.$^{-1}$ (Fig. 1). These, which are usually the most intense bands in the absorption spectrum of an aromatic hydrocarbon, are characterised by a considerable red shift at low temperature (cf. Fig. 2 for naphthalene).

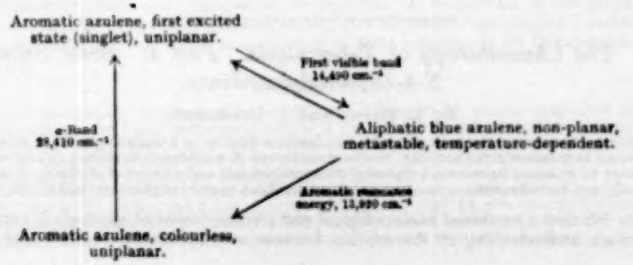
Recently (Clar, *Chem. Ber.*, 1949, **82**, 495) it has been found that the difference in frequencies between the first α- and the first β-band is equal to the difference in resonance energy between consecutive members in the anellation series, *i.e.*, the difference in resonance energy between an aromatic hydrocarbon and its preceding member in the phene series with one ring less. The application of this rule in the spectrum of azulene gives 6600 cm.$^{-1}$ or 19 kcals. for one ring. If this value is multiplied by the ratio of resonance energies of (naphthalene–benzene) : naphthalene, a resonance energy of about 40 kcals. for the whole azulene ring system is obtained. This value is also obtained by another method, as seen below.

The most striking feature of azulene is its blue colour. Investigation of the group of bands in the visible part of the spectrum shows that it has nothing in common with the other types of bands in aromatic hydrocarbons. It shifts to the ultra-violet about 120 cm.$^{-1}$ at −170°. The unusual behaviour of these bands is also shown by the strong ultra-violet shift consequent upon alkyl substitution in positions 2, 4, and 6 (see I) (Heilbronner and Wieland, *Helv. Chim. Acta*, 1947, **30**, 947). A corresponding feature is not observed in the benzenoid aromatic hydrocarbons. The intensity of these bands is doubled at −170°. The blue colour of azulene fades reversibly to a considerable degree, in high-boiling solvents such as methylnaphthalene or liquid paraffin. This shows that the blue colour of azulene originates from a metastable state, whose stability decreases with rising temperature. Corresponding metastable states are known to be formed by irradiation of aromatic hydrocarbons at low temperature in solid solution (Lewis and Kasha, *J. Amer. Chem. Soc.*, 1944, **66**, 2100; Kasha and Nauman, *J. Chem. Physics*, 1949, **17**, 516). They have life-times of several seconds. The longest life-time (about 3 minutes) was observed with triphenylene in the course of this work. It is long enough for the absorption spectrum of the yellow metastable state of the colourless triphenylene to be photographed. It shows absorption bands at 4300 and 4080 A. It is very likely that this long life-time is connected with a non-planar propeller-like state, caused by the overlapping of hydrogen atoms in the positions 1 : 4 : 5 : 8 : 9 : 12 in triphenylene (II) in solution. The blue state of azulene is, therefore,

(I.) 


(II.)

probably non-planar and might be called aliphatic azulene. In that case the aromatic resonance should have disappeared. This view is supported by the fact that the difference between the first band in the visible and the first α-band in the ultra-violet amounts to 28,410—14,490 = 13,920 cm.$^{-1}$ = 40 kcals., *i.e.*, the same value as above. The relation between the different states is therefore as follows :


Aromatic azulene, first excited state (singlet), uniplanar.
First visible band 14,490 cm.⁻¹
α-Band 28,410 cm.⁻¹
Aliphatic blue azulene, non-planar, metastable, temperature-dependent.
Aromatic resonance energy, 13,920 cm.⁻¹
Aromatic azulene, colourless, uniplanar.

From the ratio of the intensities of the bands it can be concluded that the concentration of the blue azulene amounts to a few per cent. only. Heilbronner and Wieland (*loc. cit.*) report a resonance energy of 46 kcals. for azulene. The difference of 6 kcals. can be explained by application of the Franck–Condon principle.

Recently Klevens and Platt (*J. Chem. Physics*, **1949**, **17**, 470,484; cf. Clar, *J. Chem. Physics*, **1949**, **17**, 741) used the classification of bands provided by the anellation principle for a quantum-mechanical treatment. Their classification in the case of azulene (Mann, Platt, and Klevens, *J. Chem. Physics*, **1949**, **17**, 481) has now been shown to be erroneous. They consider the visible group of bands as strongly shifted α-bands in comparison with the α-bands in naphthalene (in their terminology L_b-bands). The first ultra-violet group of bands is classified as belonging to the *p*-type (L_a-type), whilst the classification of the β-bands (B_b) is the same as in this paper. As shown above the absorption spectrum of the first two groups at low temperature contradicts this view.

There is another band (β′) of the β-type at 42,200 cm.$^{-1}$, which is probably connected with the α′-band in the same way as the β-band is with the α-band.

The technique for the low temperature-absorption was that already described (Clar, *Spectrochim. Acta*, 1950, in the press). The solvent was a mixture of 1 part of methyl alcohol and 4 parts of ethyl alcohol. The details of the absorption curve for room temperature are in good agreement with data previously recorded (Susz, St. Pfau, and Plattner, *Helv. Chim. Acta*, 1937, **20**, 469; Plattner, *ibid.*, 1941, **24**, 290; Plattner and Heilbronner, *ibid.*, 1947, **30**, 910; Heilbronner and Wieland, and Mann, Platt, and Klevens, *loc. cit.*).

Azulene (units, cm.$^{-1}$)

	at +18°.	at −170°.		at +18°.	at −170°.
Meta-stable bands	14,370	14,490	α′-Bands	33,840	33,890
	15,130	15,270			
	15,850	15,970	β-Bands	35,090	34,970
	16,610	16,720		35,710	35,460
	17,300	17,420			35,780
	18,050	18,120		36,360	36,100
	18,690	18,830			36,360
		19,420		36,970	36,770
					37,180
α-Bands	28,410	28,410		37,740	37,670
	29,410	29,370			38,310
		29,720			
		30,030	β′-Band	42,200	42,000
	30,680	30,680			
		31,060			
		31,350			
	31,950	31,800			
		32,150			
		32,570			

Naphthalene (units, cm.$^{-1}$)

	at +18°.	at −170°.
Temperature dependent α-bands	31,350	—
	31,850	31,850
α-Bands	32,150	32,240
		32,500
		32,680
		32,910
	33,220	33,190
		33,410
	33,670	33,690
		33,920
		34,190
		34,420
p-Bands	35,090	34,660
		35,150
α′-Bands	36,360	36,100
		36,630
	37,590	37,450
		38,100
	38,910	38,820
	40,320	40,160
β-Band	45,250	

I am indebted to Professor J. M. Robertson, F.R.S., for a gift of azulene.

UNIVERSITY OF GLASGOW. [*Received, March 8th*, 1950.]

369. *The Chemotherapy of Tuberculosis. Part I. Some Substituted N-4-Diphenylylamidines.*

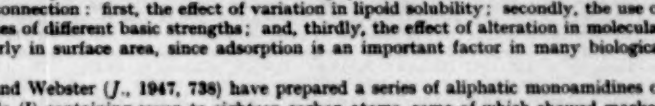
By L. BAUER and J. CYMERMAN.

In order to increase the basic strength and lipoid solubility of 4-aminodiphenyl, a substance of known anti-tuberculous activity, twelve substituted N-4-*diphenylylamidines* (V) have been prepared by reaction between a 4-diphenylylammonium salt and a series of aliphatic, aromatic, alicyclic, and hydroaromatic cyanides, and these amidines have been characterised by their *salts*.

SINCE it is felt that a combined bacteriological and physico-chemical approach is necessary for a more exact understanding of the relation between antituberculous activity and chemical

structure, an investigation into the influence of three physico-chemical factors has been undertaken in this connection: first, the effect of variation in lipoid solubility; secondly, the use of basic substances of different basic strengths; and, thirdly, the effect of alteration in molecular size, particularly in surface area, since adsorption is an important factor in many biological systems.

Newbery and Webster (*J.*, 1947, 738) have prepared a series of aliphatic monoamidines of general formula (I) containing seven to eighteen carbon atoms, some of which showed marked activities *in vitro* against *Mycobacterium tuberculosis*. In a series of publications (*Helv. Chim. Acta*, 1945, **28**, 1406; 1947, **30**, 2058; 1948, **31**, 75; 1949, **32**, 605) Erlenmeyer, Bloch, and their co-workers have compared the activities *in vitro* for a number of aromatic amines.



4-Aminodiphenyl, a lipophilic base possessing a flat surface, was taken as the starting point for this investigation. Its tuberculostatic activity was first reported by Erlenmeyer, Becker, Sorkin, Bloch, and Suter (1947, *loc. cit.*) who quote it as bacteriostatic *in vitro* in a dilution of 8×10^{-6} moles/l. Application of the above criteria to this compound led us to increase its lipoid solubility and basic strength. These properties in the case of an amine (II) may be conveniently improved by conversion into the corresponding amidine (III) (in which basic strength is greatly enhanced because of resonance possibilities; cf. Schwarzenbach and Lutz, *ibid.*, 1940, **23**, 1162), or the derived ω-dialkylaminoalkylamine, *e.g.*, (IV). A series of the latter have been synthesised and will be reported in a forthcoming communication. In this paper we report the preparation of a number of *N*-4-diphenylylamidines (V) possessing high basic strengths and containing a wide range of lipoid-solubilising substituents R.

These amidines were prepared by the elegant method of Oxley and Short (*J.*, 1946, 147), from a 4-diphenylylammonium salt and a series of aliphatic, aromatic, alicyclic, and hydroaromatic cyanides. For the preparation of aliphatic cyanides, the procedure recently given by La Forge, Green, and Gersdorff (*J. Amer. Chem. Soc.*, 1948, **70**, 3709), using ethylene glycol as solvent, proved convenient. Reaction temperatures between 100° and 185° were used, depending on the reactivity of the bromo-compound and its boiling point; and a catalytic amount of potassium iodide, added to the reaction mixture, was found to improve the yield in some cases. By this method *n*-heptyl cyanide was obtained in 86% yield from the corresponding bromide. The hydroaromatic compound, *cyclo*pent-1-enyl cyanide was obtained in 80·5% yield from the cyanohydrin.

The method of La Forge *et al.* (*loc. cit.*) failed to give *cyclo*hexyl cyanide from *cyclo*hexyl bromide. In the preparation of this cyanide by catalytic hydrogenation of *cyclo*hex-1-enyl cyanide there was also obtained a small yield of *bis*(*cyclo*hexylmethyl)amine (VI) (identified as the hydrochloride), previously obtained by Winans and Adkins (*ibid.*, 1933, **55**, 2051) from *cyclo*hexyl cyanide.

Twelve amidines (V) were obtained by fusion of a mixture of 4-diphenylylammonium benzenesulphonate or the corresponding toluene-*p*-sulphonate with cyanides of the types mentioned above. Temperatures between 180° and 250° for from 0·75 to 6 hours afforded yields ranging from 12 to 83%, and the bases obtained were characterised as their hydrochlorides, benzenesulphonates, toluene-*p*-sulphonates, or picrates. A by-product in the preparation of (V; R = *n*-$C_{16}H_{33}$) was the corresponding amide, *N*-4′-diphenylylhexadecane-1-carboxyamide. Results of bacteriological and other examinations of these compounds will be reported elsewhere in due course.

Experimental.

4-Diphenylylammonium Benzenesulphonate (A), *etc.*—Prepared by mixing equivalent amounts of 4-aminodiphenyl (in ether) and benzenesulphonic acid (in methanol), this *salt* [referred to as (*A*) below] crystallised from water in plates, m. p. 284° (Found: N, 4·3. $C_{18}H_{17}O_3NS$ requires N, 4·3%). 4-Diphenylylammonium chloride separated from water in plates, m. p. 285° (decomp.) (Found: N, 6·9. Calc. for $C_{12}H_{12}NCl$: N, 6·8%) (Hübner, *Annalen*, 1882, **209**, 342, does not give a m. p.). 4-Diphenylylammonium toluene-*p*-sulphonate formed needles (from alcohol), m. p. 249° (Found N, 4·2. Calc. for $C_{19}H_{19}O_3NS$: N, 4·1%) (Noller and Liang, *J. Amer. Chem. Soc.*, 1932, **54**, 670, give m. p. 246·6—247·6°).

N-4-Diphenylylacetamidine.—A mixture of 4-diphenylylammonium benzenesulphonate (10 g.) and methyl cyanide (15 c.c.) was heated in an autoclave for 5 hours at 180° (bath-temp.). The reaction

product was triturated with methanol–ether (1 : 10), and the residue extracted with boiling water (2 l.). Basification of the filtrate at 0° (ice) liberated the amidine which was filtered off, washed with ice-water, and dissolved in alcoholic hydrochloric acid. Evaporation of this solution and recrystallisation of the residue from acetone gave the *hydrochloride* as white plates, m. p. 180—181° (0·8 g., 12%) (Found : N, 11·5. $C_{14}H_{15}N_2Cl$ requires N, 11·4%). The *amidine* crystallised from light petroleum (b. p. 90—120°) in plates, m. p. 146—147° (Found : N, 13·4. $C_{14}H_{14}N_2$ requires N, 13·3%). The *picrate* separated from aqueous methanol or acetone–light petroleum in orange needles, m. p. 214—215°, which did not lose water of crystallisation even when dried at 115° (Found : N, 15·2, 15·0. $C_{26}H_{17}O_7N_5.H_2O$ requires N, 15·3%).

1-4′-*Diphenylylamidino*-n-*pentane*.—A solution of the salt (*A*) (5 g.) in *n*-amyl cyanide (5 g.) was refluxed for 6 hours at 220° (bath). Trituration of the cooled reaction product with ether gave the *benzenesulphonate* (3·5 g., 54%) crystallising from water in plates, m. p. 179° (Found : N, 6·7. $C_{24}H_{24}O_3N_2S$ requires N, 6·6%). The *amidine* formed flat needles [from light petroleum (b. p. 60—90°)], m. p. 124·5° (Found : N, 10·2. $C_{17}H_{20}N_2$ requires N, 10·5%). The *hydrochloride* separated from dilute hydrochloric acid (5*N*.) as needles, m. p. 231—232° (Found : N, 9·25. $C_{17}H_{21}N_2Cl$ requires N, 9·25%).

n-*Heptyl Cyanide*.—A mixture of *n*-heptyl bromide (36 g.), potassium cyanide (20 g., 1·5 mols.), and potassium iodide (1 g.) was stirred in ethylene glycol (80 c.c.) at 140° (bath) for 4 hours. The solution was diluted with water and extracted with ether. Distillation of the dried (Na_2SO_4) extracts gave *n*-heptyl cyanide (21·5 g., 86%), b. p. 102—105°/27 mm. (Newbery and Webster, *J.*, 1947, 738, give 59%, b. p. 111°/37 mm.)

1-4′-*Diphenylylamidino*-n-*heptane*.—A mixture of *n*-heptyl cyanide (11 g.) and (*A*) (10 g.) was heated at 220° (bath) for 6 hours. Dilution with ether afforded the *benzenesulphonate* (8·1 g., 59%), crystallising from acetone in needles, m. p. 158—159° (Found : N, 6·0. $C_{26}H_{29}O_3N_2S$ requires N, 6·2%). The *amidine* formed plates [from light petroleum (b. p. 60—90°)], m. p. 124° (Found : N, 9·4. $C_{20}H_{26}N_2$ requires N, 9·5%).

The *hydrochlorides* separated from water in plates, m. p. 159—160° (Found : N, 8·0, 8·2. $C_{20}H_{27}N_2Cl,H_2O$ requires N, 8·0%).

1-4′-*Diphenylylamidino*-n-*hexadecane*.—A mixture of (*A*) (9 g.) and *n*-hexadecyl cyanide (13 g.) was heated at 250° for 4·5 hours. Treatment of the cold reaction mixture with methanol precipitated *N*-4′-*diphenylylhexadecane*-1-*carboxyamide* (2·5 g., 22%), crystallising from methanol in plates, m. p. 141—142° (Found : N, 3·7. $C_{29}H_{51}ON$ requires N, 3·3%). The filtrates on dilution with water and ether gave separation of 1-4′-*diphenylylamidino*-n-*hexadecane benzenesulphonate* at the interface (5 g., 31%), m. p. 135—139°, crystallising from aqueous methanol in needles or plates, m. p. 141—143° (Found : N, 4·8. $C_{38}H_{53}O_3N_2S$ requires N, 4·8%). A solution of this salt in methanol was treated with cold methanolic potassium hydroxide solution, and then diluted with water, affording the *amidine*, crystallising from light petroleum (b. p. 40—70°) in plates, m. p. 116—119° (Found : N, 6·4. $C_{32}H_{54}N_2$ requires N, 6·7%). The *picrate* separated as yellow plates from dilute alcohol, m. p. 113—114° (Found : N, 10·7. $C_{38}H_{57}O_7N_5$ requires N, 10·8%).

cyclo*Pent*-1-*enyl Cyanide*.—A solution of *cyclo*pentanone cyanohydrin (20 g.) in chloroform (40 c.c.) was treated with thionyl chloride (30 c.c.) at such a rate that gentle ebullition took place. The solution was then refluxed until evolution of gases had ceased (3 hours). Distillation gave *cyclo*pent-1-enyl cyanide (13·5 g., 80·5%), b. p. 62°/15 mm., n_D^{25} 1·4710 (Linstead and Meade, *J.*, 1934, 956, give 67%, b. p. 69°/15 mm.).

1-4′-*Diphenylylamidino*cyclo*pent*-1-*ene*.—A solution of 4-diphenylylammonium toluene-*p*-sulphonate (13 g.) in *cyclo*pent-1-enyl cyanide (13·5 g.) was heated for 1 hour at 200° and a further hour at 180°. The dark reaction product was triturated with ether to remove unchanged cyanide, and the residue extracted with boiling water. The aqueous extract, on cooling, gave colourless plates of the *amidine toluene-p-sulphonate*, m. p. 216—218° (decomp.) (Found : N, 6·7. $C_{32}H_{32}O_3N_2S$ requires N, 6·5%). The free *amidine* crystallised from ligroin (b. p. 90—120°) in needles, m. p. 166—166·5° (Found : N, 10·7. $C_{19}H_{18}N_2$ requires N, 10·7%). The *hydrochloride* formed rhombic plates (from water), m. p. 203—205° (Found : N, 9·5. $C_{19}H_{19}N_2Cl$ requires N, 9·4%). The *picrate* separated from acetone–light petroleum in yellow prisms, m. p. 147—148° (decomp.) (Found : N, 13·7. $C_{25}H_{21}O_7N_5$ requires N, 14·25%).

1-4′-*Diphenylylamidino*cyclo*hex*-1-*ene*.—A mixture of 4-diphenylylammonium toluene-*p*-sulphonate (34 g.) and *cyclo*hex-1-enyl cyanide (22 g., 2 mols.) was heated at 200—210° for 2 hours. The cooled melt was triturated with acetone and ether, and the residue (37 g., 83%) crystallised from methanol–ether as white needles, m. p. 248° (22 g., 50%) of the *amidine toluene*-p-*sulphonate* (Found : N, 6·3. $C_{33}H_{34}O_3N_2S$ requires N, 6·3%). The free *amidine* separated from light petroleum (b. p. 60—90°) in clusters of white needles, m. p. 141—142° (Found : N, 10·0. $C_{20}H_{20}N_2$ requires N, 10·1%). The *hydrochloride* formed flat needles (from 5*N*-hydrochloric acid), m. p. 231—232° (decomp.) (Found : N, 9·0. $C_{20}H_{21}N_2Cl$ requires N, 9·0%), and the *benzenesulphonate* was obtained in feathery needles, m. p. 232—233° (decomp.) (Found : N, 6·8. $C_{32}H_{32}O_3N_2S$ requires N, 6·5%). The *picrate* separated from acetone–light petroleum in yellow needles, m. p. 184—185° (Found : N, 13·7. $C_{32}H_{23}O_7N_5$ requires N, 13·9%).

cyclo*Hexyl Cyanide*.—Distillation of the product obtained by hydrogenation of *cyclo*hex-1-enyl cyanide (13·5 g.) in methanol (200 c.c.) using a platinic oxide catalyst gave *cyclo*hexyl cyanide (5 g., 31%), b. p. 72—73°/16 mm., n_D^{15} 1·4543 (Grignard, Bellet, and Courtot, *Ann. Chim.*, 1919, **12**, 368, give 50%, b. p. 75—77°/16 mm., n_D^{20} 1·453), followed by bis*cyclo*hexylmethylamine, b. p. 160°/16 mm., which gives a hydrochloride, m. p. 293° (decomp.), as rhombic plates from dilute hydrochloric acid (Found : C, 68·7; H, 11·3; N, 6·1. Calc. for $C_{14}H_{32}NCl$: C, 68·4; H, 11·5; N, 5·7%) (Winans and Adkins, *J. Amer. Chem. Soc.*, 1933, **55**, 2051, give b. p. 150—155°/14 mm. for the base and m. p. 298—299° for the salt).

1-4′-*Diphenylylamidino*cyclo*hexane*.—*cyclo*Hexyl cyanide (5 g.) and 4-diphenylylammonium toluene-*p*-sulphonate (12 g.) were heated together for 3 hours at 200°. The product was taken up in methanol and treated with ether, giving the *amidine toluene*-p-*sulphonate* (12·3 g., 78%), m. p. 200—205°, crystallising from isopropanol–ether in colourless prisms, m. p. 206° (Found : N, 5·9. $C_{33}H_{36}O_3N_2S$

requires N, 6·2%). The free *amidine* separated from light petroleum (b. p. 90—100°) in tufts of needles, m. p. 161° (Found: N, 10·0. $C_{19}H_{20}N_2$ requires N, 10·1%). The *hydrochloride* crystallised from alcohol–ether in rhombs, m. p. 223—225° (decomp.) (Found: N, 7·95, 8·05. $C_{19}H_{20}N_2Cl,2H_2O$ requires N, 8·0%).

N-4-Diphenylylbenzamidine.—A solution of (*A*) (6·6 g.) in phenyl cyanide (5 c.c.) was refluxed at 220° for 4½ hours. Treatment of the cooled mixture with acetone gave the *benzenesulphonate* (4 g., 46%) crystallising from water as lustrous plates, m. p. 218—219° (Found: N, 6·5. $C_{25}H_{24}O_3N_2S$ requires N, 6·5%). The *amidine* crystallised from chloroform–light petroleum (b. p. 30—60°) in flat needles, m. p. 185° (Found: N, 10·4. $C_{19}H_{16}N_2$ requires N, 10·3%). The *hydrochloride* separated from alcohol–ether in colourless crystals, m. p. 233—234° (Found: N, 9·1. $C_{19}H_{17}N_2Cl$ requires N, 9·1%).

p-Chloro-N-4′-diphenylylbenzamidine.—Fusion of *p*-chlorophenyl cyanide (2·5 g.) and 4-diphenylylammonium toluene *p*-sulphonate (5·5 g.) at 200° for 0·75 hour and treatment of the cooled reaction mixture with methanol and ether gave the *amidine toluene-p-sulphonate* (5·9 g., 76%), crystallising from *iso*propanol or water in plates, m. p. 266—267° (Found: N, 5·9. $C_{26}H_{23}O_3N_2SCl$ requires N, 5·9%). The free *amidine* separated from chloroform in colourless rhombs, m. p. 216—217° (Found: N, 9·0. $C_{19}H_{15}N_2Cl$ requires N, 9·1%). The *hydrochloride* formed rhombs (from alcohol–ether), m. p. 279° (decomp.) (Found: N, 8·2. $C_{19}H_{17}N_2Cl_3$ requires N, 8·2%).

p-Ethoxy-N-4′-diphenylylbenzamidine.—A mixture of (*A*) (3·3 g.) and *p*-ethoxyphenyl cyanide (2 g.) was heated at 220° for 4 hours. Cooling and trituration with acetone gave the *benzenesulphonate* (2·5 g., 52%) crystallising from water in plates, m. p. 232—234° (Found: N, 6·0. $C_{27}H_{26}O_4N_2S$ requires N, 5·9%). The *amidine* separated from ethyl acetate in lustrous plates, m. p. 217—218° (Found: N, 9·0. $C_{21}H_{20}ON_2$ requires N, 8·9%), and the *hydrochloride* formed hexagonal plates (from water), m. p. 266—267° (decomp.) (Found: N, 7·7. $C_{21}H_{21}ON_2Cl$ requires N, 7·9%).

3 : 4-Dimethoxy-N-4′-diphenylylbenzamidine.—3 : 4-Dimethoxyphenyl cyanide (2·8 g.) and 4-diphenylylammonium toluene-*p*-sulphonate (5·1 g.) were fused at 200° for 2 hours. Working up of the cooled melt afforded the *amidine toluene-p-sulphonate* (5·8 g., 77%), crystallising from *iso*propanol in colourless rhombs, m. p. 217—218° (Found: N, 5·6. $C_{29}H_{28}O_5N_2S$ requires N, 5·6%). The *amidine* crystallised from chloroform–light petroleum (b. p. 40—70°) in needles, m. p. 206—207° (Found: N, 8·5. $C_{23}H_{24}O_2N_2$ requires N, 8·4%), and the *hydrochloride* formed needles, m. p. 230—232° (Found: N, 7·0. $C_{23}H_{21}O_2N_2Cl,2H_2O$ requires N, 6·9%).

p-Carbethoxy-N-4′-Diphenylylbenzamidine.—A mixture of *p*-carbethoxyphenyl cyanide (2·5 g.) and (*A*) (3·5 g.) was heated at 220° for 0·75 hour. The cooled melt was extracted with hot methanol (150 c.c.), and the insoluble *benzenesulphonate* (1·8 g., 34%) filtered off and crystallised from *iso*propanol, forming colourless rhombs, m. p. 250—251° (Found: N, 5·8, 5·9. $C_{32}H_{32}O_5N_2S$ requires N, 5·6%). The methanolic filtrates on treatment with methanolic potassium hydroxide gave the *amidine* (0·8 g., 22%), separating from alcohol in rhombs, m. p. 187—188° (Found: N, 8·3, 8·3. $C_{28}H_{28}O_2N_2$ requires N, 8·1%). Treatment of the base with alcoholic hydrogen chloride and ether yielded the *hydrochloride*, m. p. 216—217° (Found: N, 6·8, 6·75. $C_{28}H_{31}O_3N_2Cl,2H_2O$ requires N, 6·75%).

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370. *The Apparent Polarities of a Number of Substituted Chloro-, Nitro-, Methyl-, Methoxy-, and Acetyl-benzenes.*

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The apparent dipole moments, in benzene at 25° (refractivity method), of some 19 substances are recorded. When the aromatic nucleus has three or more substituent groups the molecular polarities cannot be predicted accurately or explained generally by any one alone of a number of qualitative treatments, already described in, or indicated by, the literature.

The Barclay–Le Fèvre relation (*J.*, 1950, 556) is found to provide, from data for benzene solutions, a satisfactory estimate of the moments, as measured in the gaseous state, of anisole and acetophenone.

KADESCH AND WELLER (*J. Amer. Chem. Soc.*, 1941, **63**, 1310) have reported the dipole moment of acetylmesitylene as 2·71 D. and attributed the difference between this figure and that found by them for acetophenone, *viz.*, 2·88 D., to steric inhibition of mesomerism (cf. Birtles and Hampson, *J.*, 1937, 10; Ingham and Hampson, *J.*, 1939, 981). The purpose of the present communication is to put on record a number of determinations, of which that for acetylmesitylene was one, started at University College, London, during 1935—39, to compare the moments of various monosubstituted benzene derivatives with those of derivatives which, by crude vectorial arguments based on a regular hexagonal C_6 skeleton, should have had the same values. The work was originally suggested by suppositions (Le Fèvre and Le Fèvre, *J.*, 1935, 957) which,

after the appearance of Hampson's papers, seemed much less necessary. Our results may, however, have a residual usefulness. They are given in Table I below, together with figures for a few related substances. Benzene has been the solvent throughout.

TABLE I.

Compound.	$_{\infty}P_2$ (c.c.).	$[R_L]_D$.	$_{\infty}P_2 - [R_L]_D$.	Apparent D.	Source.
(A) *Anisole series.*					
Anisole	67·4	33·0 *	34·4	1·3$_5$	Present work.
3-Methyl-6-*tert.*-butylanisole	96·0	56·6 †	39·4	1·3$_5$	"
p-Nitroanisole	515·0	39·6 ‡	475·4	4·8$_3$	"
2 : 4 : 6-Trinitroanisole	134·6	50·6 †	84·0	2·0$_3$	"
" Musk Ambrette "	315·3	67·3 †	248·0	3·4$_4$	"
(B) *Toluene series.*					
Toluene	33·5	31·1 *	2·4	(0·3$_4$)	*J.*, 1935, 480.
2 : 4 : 6-Trichlorotoluene	54·9	46·1 †	8·8	0·6$_4$	Present work
2 : 4 : 6-Trinitrotoluene	87·2	48·7 †	38·5	1·3$_7$	"
Mesitylene	41·8	40·6 *	1·2	(0·2$_4$)	"
Nitromesitylene	329·4	47·0 §	282·4	3·7$_1$	"
Trinitromesitylene	70·5	59·2	11·3	(0·7$_4$)	*J.*, 1935, 957
5-*tert.*-Butyl-*m*-xylene	56·5	55·2	1·3	(0·2$_4$)	*J.*, 1935, 488
2 : 4 : 6-Trinitro-5-*tert.*-butyl-*m*-xylene	98·5	72·2	26·3	1·1$_4$	*J.*, 1935, 957
(C) *Chlorobenzene series.*					
Chlorobenzene	83·3	31·1 *	52·2	1·60	*Trans. Faraday Soc.*, 1950, **46**, 1
1 : 4-Dichlorobenzene	37·7	36·2 §	1·5	(0·27)	*J.*, 1936, 487
1 : 3 : 5-Trichlorobenzene	42·8$_5$	40·9 §	1·9$_5$	(0·31)	Present work
1-Chloro-2 : 4-dinitrobenzene	258·2	43·0 †	215·2	3·2$_4$	"
Picryl chloride	74·8	48·8 †	26·0	1·1$_3$	"
(D) *Acetophenone series.*					
Acetophenone	217·1	36·3 *	170·8	2·8$_9$	"
4-Methylacetophenone	255·2	40·9	214·3	3·2$_3$	"
2 : 4 : 6-Trimethylacetophenone	209·9	50·8 †	159·1	2·7$_1$	"
3 : 5-Dinitro-2 : 6-dimethyl-4-*tert.*-butylacetophenone	228·2	74·8	153·4	2·7$_4$	"
3-Nitro-4-methylacetophenone	298·9	46·8	152·1	2·7$_1$	"
(E) *Nitrobenzene series.*					
Nitrobenzene	356·1	32·7 *	323·4	3·97	*Trans. Faraday Soc.*, 1950, **46**, 1
1 : 3-Dinitrobenzene	344·7	38·6	306·1	3·8$_4$	Present work
1 : 3 : 5-Trinitrobenzene	54·3	44·7	9·6	(0·6$_4$)	*J.*, 1935, 957
2 : 5-Dichloronitrobenzene	290·0	42·5(2)	247·5	3·48	Present work

* From Landolt-Bornstein-Roth, " Tabellen," 4th Edn., p. 1027. † Calc. from the preceding asterisked datum, by using the group refractivities listed by Vogel, *J.*, 1948, 1842.

‡ Calc. from figures for anisole and nitrobenzene, together with $C_6H_5 = 26·2$ and H = 1·1.

§ Thomson, *J.*, 1944, 404. ‖ Tiganik, *Z. physikal. Chem.*, 1931, *B*, **13**, 425.

Comparison with Previous Measurements.—Nitro- and chloro-benzene have been frequently studied (cf. Cleverdon and Smith, *Trans. Faraday Soc.*, 1949, **45**, 109; Le Fèvre, *ibid.*, 1950, **46**, 1, for references). Where several of the remaining compounds are concerned previous data were not always consistent; these cases are summarised in Table II and may be compared with our values, shown by asterisks. It should be noted that, in our calculations, we have used the latest values for Avogadro's number and Boltzmann's constant (Birge, *Reports Prog. Physics*, 1941, **8**, 126; *J.*, 1946, 219). The conversion of earlier dipole-moment values to our basis requires multiplication by 1·006.

Discussion.—In a general way it is obvious that substitution in the positions *ortho*- to groups such as methoxy, nitro, etc., may effect the configurations of the latter and so, by induction, inhibition of resonance, or valence deflection, influence the resultant molecular moment of the derivative. Much more experimental evidence will be needed before the " weights " of these causes can be assessed, and the position at present is still as stated by Watson (*Ann. Reports*, 1939, **36**, 215; 1942, **38**, 124) in the concluding paragraph of his review of the various manifestations of the " *ortho*-effect." Indeed, where the polarities now recorded are concerned there are two further complications: (*a*) that recent work (Bastiansen and Hassel, *Acta Chem.*

Scand., 1947, **1**, 489; cf. Angus, Bailey, Hale, Ingold, Leckie, and Raison, *J.*, 1936, 971) suggests that valency deflections above or below—as well as in—the C_6 plane may occur when adjacent positions are highly crowded, and (*b*) that, especially with *s*-trinitro-derivatives, the "refractivity" method of calculation, applied in Table I, fails to make adequate allowance for the atomic polarisations (cf. Sutton, *Ann. Reports*, 1940, **37**, 57), so that for the 1 : 3 : 5-trinitro-derivatives of benzene and mesitylene apparent moments *ca.* 0·7 D. are indicated. Yet if this figure be applied as a "correction" in the cases of picryl chloride, T.N.T., trinitrobutylxylene, and trinitroanisole, only with the last is there no excess over the moment of the un-nitrated compound.

Solvent Influences with Anisole and Acetophenone.—The moments of these two molecules have been determined in the gaseous state by Groves and Sugden (*J.*, 1937, 1782; *J.*, 1935, 971) as 1·35 and 3·00 D. respectively. From the worked example (ether) shown in the 1937 paper it seems that these figures, before incorporation with our present data into $\mu^2_{solution}/\mu^2_{gas}$ ratios, should also (see above) be multiplied by 1·006. After this adjustment, they become 1·36 and 3·02 D.

TABLE II.

Anisole. 0·8 [1], 1·16 [2], 1·23 [3], 1·22 [4], 1·28 [5], 1·30 [6].
p-Nitroanisole. 4·36 [6], 4·78 [7], 4·74 [8], 4·52 [6].
2 : 4 : 6-Trichlorotoluene. 0·57 [9], $(0·6_4)$ [6].
Nitromesitylene. 3·67 [10], 3·64 [11], 3·7 [6].
1 : 3 : 5-Trichlorobenzene. 0·28 [12], 0·31 [6].
1-Chloro-2 : 4-dinitrobenzene. 3·29 [13], 3·00 [14], $3·2_5$ [6].
Acetophenone. 2·97 [15], 2·85 [17], 2·96 [15], 2·96 [16], 2·89 [6].
4-Methylacetophenone. 3·23 [15], $3·2_5$ [6].
2 : 4 : 6-Trimethylacetophenone. 2·71 [17], 2·81 [18], 2·79 [6].
1 : 3-Dinitrobenzene. 4·02 [20], 3·70 [20], 3·81 [21], 3·75 [20], 3·96 [22], 3·86 [6].
2 : 5-Dichloronitrobenzene. 3·45 [24], 3·45 [25], $3·4_4$ [6].

[1] Estermann, *Z. physikal. Chem.*, 1928, *B*, **1**, 134. [2] Højendahl, Thesis, Copenhagen, 1928, p. 105. [3] Donle and Volkert, *Z. physikal. Chem.*, 1930, *B*, **8**, 60. [4] Phadke, Gokhale, Phalniker, and Bhide, *J. Indian Chem. Soc.*, 1945, **22**, 235. [5] Everard and Sutton, *J.*, 1949, 2312. [6] Ref. 2, p. 106. [7] Donle and Gehrckens, *Z. physikal. Chem.*, 1932, *B*, **18**, 316. [8] Cowley and Partington, *J.*, 1933, 1258. [9] Maryott, Hobbs, and Gross, *J. Amer. Chem. Soc.*, 1940, **62**, 2320. [10] Hammick, New, and Williams, *J.*, 1934, 29. [11] Brown, de Bruyne, and Gross, *J. Amer. Chem. Soc.*, 1934, **56**, 1291. [12] Tiganik, *Z. physikal Chem.*, 1931, *B*, **13**, 425. [13] Hassel and Naeshagen, *ibid.*, p. 79. [14] Lütgert, *ibid.*, 1932, *B*, **17**, 460. [15] Hassel and Naeshagen, *ibid.*, 1929, *B*, **4**, 217; Hassel and Uhl, *ibid.*, 1930, *B*, **8**, 187. [16] Fuchs and Donle, *ibid.*, 1933, *B*, **22**, 1. [17] Kadesch and Weller, *J. Amer. Chem. Soc.*, 1941, **63**, 1310. [18] Cherrier, *Compt. rend.*, 1947, **225**, 1306. [20] Bentley, Everard, Marsden, and Sutton, *J.*, 1949, 2957. [20] Ref. 2, pp. 85—89. [21] Williams, *Physikal. Z.*, 1928, **29**, 174; Williams and Schwingel, *J. Amer. Chem. Soc.*, 1928, **50**, 362. [22] Ref. 12. [24] Higasi, *Bull. Inst. Phys. Chem. Res. Japan*, 1941, **20**, 218. [25] Ref. 13. [25] Thomson, *J.*, 1944, 404.

TABLE III.

	n^{20}_D.	Exp. α^2.	$\mu_{C_6H_5}$.	(μ_{gas}), calc.	(μ_{gas}), found.
Anisole	1·5147	0·664	1·30	1·36	1·36
Acetophenone	1·5308	0·590	2·89	3·06	3·02

As a further test of its usefulness, the Barclay–Le Fèvre relation (*J.*, 1950, 556) has been applied (Table III) to anisole and acetophenone on the assumptions that both molecules are planar and that $\mu_{resultant}$ bisects a C–O–Me angle of 110° in one case and acts collinearly with the C=O link in the other. Details are explained in the reference just cited; $(n^2_D)^{20}_{C_6H_5}$ is taken as 2·2417.

Agreement between prediction and experiment is satisfactory. With the exception of certain amines (cf. Barclay and Le Fèvre, *Trans. Faraday Soc.*, in the press) these are the first structures having moments off an axis of symmetry, upon which the new equation has been tried.

It will be noted that $\delta\mu(= \mu_{calc.} - \mu_{gas})$ is, for anisole, −0·06, and for acetophenone, −0·13 D., *viz.*, approximately as 1 : 2. According to Leiser (*Abh. Disch. Bunsen-Ges.*, 1910, 67) these two substances have electric double refractions related as *ca.* 1 : 57, so that—as with aniline (Le Fèvre, Roberts, and Smythe, *J.*, 1949, 902) or methylene dichloride (Barclay and Le Fèvre, *J.*, 1950, 556)—neither the sign nor the magnitude of this property is necessarily a good guide to the type of solvent action to be expected (cf. also, Le Fèvre and Ross, *J.*, 1950, 283).

EXPERIMENTAL.

Materials.—Unless otherwise stated, these were commercial specimens. Anisole was dried over phosphoric oxide and distilled; it had b. p. 153—154°/*ca.* 750 mm. 3-Methyl-5-*tert.*-butylanisole, from

isobutyl bromide, *m*-tolyl methyl ether, and aluminium chloride (Baur, *Ber.*, 1894, **27**, 1616), was collected at 220—225°/758 mm. *p*-Nitroanisole, crystallised from light petroleum, had m. p. 51°. 2 : 4 : 6-Trinitroanisole, from picryl chloride and sodium methoxide (Brady and Horton, *J.*, 1925, 2230), had m. p. 68° after two crystallisations (methyl alcohol). "Musk Ambrette" (Baur, D.R.P. 62,362/1891; for constitution see Fuson *et al.*, *J. Org. Chem.*, 1947, **12**, 587), recrystallised several times from alcohol, had m. p. 63°. 2 : 4 : 6-Trichlorotoluene, prepared following Cohen and Dakin (*J.*, 1902, **81**, 1335), had m. p. 33° after distillation. Mesitylene was purified as described by Le Fèvre (*J.*, 1933, 980) for *p*-cymene and had b. p. 163—164°, d_4^{20} 0·8595, n_D^{20} 1·4969. Nitromesitylene, prepared by the method of *Org. Synth.*, **14**, 68, had m. p. 44° (from methyl alcohol). T.N.T., recrystallised from nitric acid and subsequently from a benzene–ethanol mixture, melted at 82°. Baur's directions (*Ber.*, 1891, **24**, 2840) afforded 5-*tert.*-butyl-*m*-xylene, b. p. 203°/759 mm. Trichlorobenzene, m. p. 63—64°, was obtained from 2 : 4 : 6-trichloroaniline (Jackson and Lamar, *Amer. Chem. J.*, 1896, **18**, 667). 1-Chloro-2 : 4-dinitrobenzene had m. p. 50—51° (from ether). Picryl chloride, prepared from picric acid by the method of Gazzolo and Jackson (*Amer. Chem. J.*, 1900, **23**, 384; cf. Brady and Horton, *loc. cit.*) and recrystallised from ligroin, had m. p. 83°. Acetophenone, dried over calcium chloride, was distilled immediately before use, and had b. p. 200°/758 mm. 4-Methylacetophenone, from toluene, etc. (cf. Adams and Noller, *J. Amer. Chem. Soc.*, 1924, **46**, 1889), was treated similarly to the previous substance, and had b. p. 225°/736 mm. Trimethylacetophenone (Noller and Adams, *loc. cit.*) had b. p. 123°/20 mm. Dinitrodimethyl-*tert.*-butylacetophenone was a specimen of "Musk ketone" with m. p. 135—136° (Baur, *Ber.*, 1898, **31**, 1344, gives 136°) after successive crystallisations from acetic acid and alcohol. 3-Nitro-4-methylacetophenone, prepared by direct nitration (cf. Errera, *Gazzetta*, 1891, **21**, 92), had m. p. 61° (from light petroleum). 1 : 3-Dinitrobenzene had m. p. 89—90°, and 2 : 5-dichloronitrobenzene, m. p. 55—56° (both from alcohol; cf. Cohen and Bennett, *J.*, 1905, **87**, 322, for the second compound). Benzene (as solvent) was AnalaR material to which sodium wire had been added, and one-third frozen, decanted, remelted, and left for 2 days before use.

Measurements.—These have involved the resonance circuits of Le Fèvre and Russell (*Trans. Faraday Soc.*, 1947, **43**, 374), and the simpler arrangement now in use in Sydney (cf. Calderbank and Le Fèvre, *J.*, 1948, 1949). Data are set out below under the usual symbols (cf. "Dipole Moments," Methuen, 1938, Chap. II). Those cases where the concentrations are shown as molar fractions (f_1) are our earliest observations, taken in 1935—36. For uniformity, we have calculated dielectric constants and densities relatively to benzene (ϵ^{25} = 2·2725 and d_4^{25} = 0·87378). When $\alpha\epsilon_2$ or βd_2 has appeared non-rectilinear with composition, the extrapolation procedure of Le Fèvre (*Trans. Faraday Soc.*, 1950, **46**, 1) has been adopted.

Anisole.

10^4w_1	1223	1891	2551	5692	9148
ϵ^{25}	2·2933	2·3067	2·3171	2·3727	2·4389
d_4^{25}	0·87533	0·87618	0·87705	0·88107	0·88540
P_1 (c.c.)	65·8$_6$	67·9$_1$	66·5$_8$	66·1$_7$	66·7$_0$

Mean $\alpha\epsilon_2$ = 1·76$_4$; mean βd_2 = 0·127$_4$.

p-*Nitroanisole.*

10^4w_1	1025	1046	2543	3114	3186
ϵ^{25}	2·4434	2·4471	2·7001	2·7982	—
d_4^{25}	0·87619	0·87625	0·87976	0·88110	0·88128
P_1 (c.c.)	498·2	498·3	475·0	467·2	—

$(\alpha\epsilon_2)_{w_1=0}$ = 16·5$_2$ (graphically); βd_2 is approximately constant, mean = 0·2353.

2 : 4 : 6-*Trinitroanisole.*

10^4f_1	2622·5	8002·3	13,160	14,501
ϵ^{25}	2·2882	2·3211	2·3532	2·3608
d_4^{25}	0·87680	0·88345	0·88993	0·89164
P_1 (c.c.)	134·5	134·2	134·1	133·2

$_\infty P_1$ (graphically) = 134·6 c.c.

3-*Methyl*-5-*tert.*-*butylanisole.*

10^4w_1	11,462	15,144	19,244	29,593
ϵ^{25}	2·3053	2·3166	2·3269	2·3564
d_4^{25}	0·87608	0·87694	0·87789	0·87996
P_1 (c.c.)	96·8	96·1	95·9	94·1

Mean $\alpha\epsilon_2$ = 2·85$_2$; mean βd_2 = 0·208$_4$.

2 : 4-*Dinitro*-3-*methyl*-6-*tert.*-*butylanisole* ("*Musk Ambrette*").

10^4w_1	27,224	46,115	48,947	69,547
ϵ^{25}	2·4116	2·5121	2·5278	2·6411
d_4^{25}	0·88102	0·88570	0·88650	0·89168
P_1 (c.c.)	311·3	309·4	309·2	306·1

$(\alpha\epsilon_2)_{w_1=0}$ = 4·98 graphically; mean βd_2 = 0·260$_2$.

2 : 4 : 6-*Trichlorotoluene.*

10^4w_1	9861	12,135	20,661
ϵ^{25}	2·2757	2·2765	2·2793
d_4^{25}	0·87686	0·87756	0·88022
P_1 (c.c.)	54·8	55·0	55·0

$\Sigma(\epsilon_{12} - \epsilon_2)/\Sigma w_1$ = 0·3281; $\Sigma(d_{12} - d_2)/\Sigma w_1$ = 0·311$_4$.

2 : 4 : 6-*Trinitrotoluene.*

10^4f_1	1883	3220	5420
ϵ^{25}	2·2786	2·2822	2·2886
d_4^{25}	0·87596	0·87750	0·88001
P_1 (c.c.)	90·6	86·8	86·2

$\Sigma(P_{12} - P_2)/\Sigma f_1$ = 60·64, whence $_\infty P_1$ = 87·2$_2$ c.c.

Mesitylene.

10^4w_1	32,061	54,882
ϵ^{25}	2·2710	2·2703
d_4^{25}	0·87250	0·87158
P_1 (c.c.)	41·7	41·9

Nitromesitylene.

10^4w_1	1012	2391	2613
ϵ^{25}	2·3658	2·5090	2·5111
d_4^{25}	0·87545	0·87805	0·87809
P_1 (c.c.)	325·1	312·8	312·7

Mean $\alpha\epsilon_2$ = 9·14$_4$; mean βd_2 = 0·164$_4$.

2 : 4 : 6-*Trichlorobenzene.*

10^4w_1	1019	1130	2098
ϵ^{25}	2·2737	2·2739	2·2759
d_4^{25}	0·87711	0·87747	0·87863
P_1 (c.c.)	42·8	43·1	42·7

Mean $\alpha\epsilon_2$ = 0·120$_1$; mean βd_2 = 0·326$_4$.

1-Chloro-2 : 4-dinitrobenzene.

10^4w_1 ...	6215	7316	8241	9918
ϵ^{25}	2·3080	2·3149	2·3205	2·3303
d_4^{25}	0·87624	0·87689	0·87705	0·87771
P_1 (c.c.)	253·1	296·5	256·3	255·9

Mean $\alpha\epsilon_1 = 5·79$; mean $\beta d_1 = 0·396_5$.

Picryl chloride.

10^4f_1 ...	2245	3216	6197	6295
ϵ^{25}	2·2768	2·2796	2·2883	2·2889
d_4^{25}	0·8789	0·8784	0·8828	0·8829
P_1 (c.c.)	71·0	73·6	77·6	73·8

$\Sigma(P_{12} - P_2)/\Sigma f_1 = 48·2$, whence ∞P_1 = 74·8 c.c.

Acetophenone.

10^4w_1 ...	801·2	1986	2113	3292	3301
ϵ^{25}	2·3342	2·4314	2·4394	2·5255	2·5333
d_4^{25}	0·87389	0·87649	0·87666	0·87815	0·87829
P_1 (c.c.)	211·7	208·3	205·7	202·2	201·9

Mean $\alpha\epsilon_1 = 8·08$; mean $\beta d_1 = 0·136_5$.

4-Methylacetophenone.

10^4w_1 ...	8135	11,312	16,215
ϵ^{25}	2·3421	2·3692	2·4111
d_4^{25}	0·87474	0·87511	0·87569
P_1 (c.c.)	251·6	250·1	247·8

$\Sigma(\epsilon_{12} - \epsilon_2)/\Sigma w_1 = 8·55$;
$\Sigma(d_{12} - d_2)/\Sigma w_1 = 0·117_5$.

2 : 4 : 6-Trimethylacetophenone.

10^4w_1 ...	9981	11,561	12,889	13,102	21,951	32,501
ϵ^{25}	2·3225	2·3335	2·3415	2·3426	2·3823	2·4448
d_4^{25}	0·87432	0·87460	0·87473	0·87475	0·87538	0·87628
P_1 (c.c.)	202·6	209·1	211·1	210·9	199·0	205·3

$\Sigma(\epsilon_{12} - \epsilon_2)/\Sigma w_1 = 5·22$; $\Sigma(d_{12} - d_2)/\Sigma w_1 = 0·072_4$.

3 : 5-Dinitro-2 : 6-dimethyl-4-tert.-butylacetophenone.

10^4f_1 ...	3801·0	8525·0	12,777	15,119
ϵ^{25}	2·3126	2·3622	2·4058	2·4302
d_4^{25}	0·87728	0·88161	0·88550	0·88762
P_1 (c.c.)	226·8	225·5	223·5	223·1
n_D * ...	—	—	1·49828	1·49875
R_1 (c.c.)	—	—	74·9	74·8

∞P_1 (graphically) = 228·2 c.c.

* The benzene used had $n_D = 1·49733$.

3-Nitro-4-methylacetophenone.

10^4f_1 ...	3695·4	4352·1	7689·6	8155·4
ϵ^{25}	0·3348	2·3451	2·3991	2·4065
d_4^{25}	0·87560	0·87593	0·87758	0·87777
P_1	920·9	287·8	282·0	281·4

∞P_1 (graphically) = 298·9 c.c.

1 : 3-Dinitrobenzene.

10^4w_1 ...	6176	9018	10,299	16,927	19,957
ϵ^{25}	2·3333	2·3614	2·3741	2·4402	2·4705
d_4^{25}	0·87590	0·87689	0·87733	0·87967	0·88075
P_1 (c.c.)	340·8	338·3	338·1	333·9	331·8

$(\alpha\epsilon_1)_{w_1=0} = 9·80$; $(\beta d_1)_{w_1=0} = 0·340_5$.

(Both by graphical extrapolation.)

2 : 5-Dichloronitrobenzene.

10^4w_1	10,123	12,105	17,501	25,131	30,021
ϵ^{25}	2·3416	2·3548	2·3898	2·4376	2·4673
d_4^{25}	0·87764	0·87840	0·88046	0·88337	0·88524
P_1 (c.c.)	278·4	276·6	270·9	263·1	258·5

$(\alpha\epsilon_1)_{w_1=0} = 7·01$ (graphically); βd_1 (average) $= 0·381_5$.

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371. *Contributions to the Chemistry of* isoQuinolines. *Part II. The Synthesis of Chloro-amino-phenylisoquinolines in a Search for New Trypanocides.*

By A. McCOUBREY.

In furtherance of earlier studies (*J.*, 1949, 696) and by similar methods, 7-amino-1-*p*-chlorophenyl- and 7-chloro-1-*p*-aminophenyl-*iso*quinoline methiodides have been synthesised. They showed no noteworthy biological activity.

In Part I (*J.*, 1949, 696) it was shown that nitration of 3 : 4-dihydro*iso*quinolines introduced a nitro-group at the 7-position. This substitution appeared to lend itself readily to the synthesis of 7-chloro*iso*quinolines which are of interest in view of the occurrence of the *p*-chlorophenyl group in a number of biologically active products.

The required 3 : 4-dihydro*iso*quinolines were obtained by Bischler–Napieralski cyclisation of the requisite carboxyamides in toluene or tetralin by means of phosphoric oxide, *viz.*, *p*-chlorobenzo-2-phenylethylamide to 1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline, *N*-*p*-chlorobenzo-2-*p*-chlorophenylethylamide to 7-chloro-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline, *N*-*p*-nitro-

benzo-2-*p*-chlorophenylethylamide to 7-chloro-1-*p*-nitrophenyl-3 : 4-dihydro*iso*quinoline. In addition, 4-chloro-3-nitrobenzo-2′-phenylethylamide was cyclised to 1-(4′-chloro-3′-nitrophenyl)-3 : 4-dihydro*iso*quinoline during investigations into the structure of nitration products.

Nitration of 1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline under mild conditions has been found to occur at the 7-position since reduction of the product to the amine, followed by a Sandmeyer reaction, gave 7-chloro-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline, identical with the product of cyclisation of *p*-chlorobenzo-2-*p*-chlorophenylethylamide. Further nitration introduced a second nitro-group to give a product, also obtained in one step by use of a stronger nitrating mixture, identical with the nitration product of 1-(4′-chloro-3′-nitrophenyl)-3 : 4-dihydro*iso*quinoline, thus establishing the point of entry of this second nitro-group.

The 3 : 4-dihydro*iso*quinolines were dehydrogenated by palladium black to the *iso*quinolines, which were either reduced to the corresponding amines, or were methylated, before reduction, to give the corresponding quaternary salts. 1-*p*-Aminophenyl*iso*quinoline (Gilman and Gainer, *J. Amer. Chem. Soc.*, 1947, **69**, 1946) and its methiodide were similarly prepared from 1-*p*-nitrophenyl*iso*quinoline.

None of these bases or quaternary salts showed noteworthy activity against *Trypanosoma equiperdum*, *T. congolense*, or *Entamœba histolytica*.

Experimental.

p-Chlorophenylethylamine.—*β-p*-Chlorophenylpropionic acid (Shoppee, *J.*, 1930, 976) (80 g.) was refluxed with thionyl chloride (80 c.c.) for 3 hours and excess of thionyl chloride was removed under reduced pressure. The product was added portion-wise to a stirred solution of sodium azide (56 g.) in 50% acetone (1 l.) maintained at 0°, and the mixture, which separated into two layers, was extracted with benzene. The benzene extract was thoroughly dried ($CaCl_2$) at 0° and was then refluxed until nitrogen evolution ceased. Hydrochloric acid (*d* 1·16; 80 c.c.) was added and refluxing continued until carbon dioxide evolution ceased. The amine hydrochloride which separated was redissolved in water, and the benzene separated. The aqueous layer was basified and the amine extracted with ether. The extract was dried (K_2CO_3) and distilled, yielding a colourless oil (62·6 g., 92·8%), b. p. 125—130°/10 mm. Buch (*J. Amer. Chem. Soc.*, 1933, **55**, 2503) obtained a 50% yield by catalytic reduction of carbomethoxy-*p*-chloromandelonitrile. The *toluene*-*p*-*sulphonate* crystallised from alcohol in white plates, m. p. 235° (Found: N, 4·2; Cl, 11·1. $C_{15}H_{16}O_3NClS$ requires N, 4·5; Cl, 11·5%).

N-*Acyl*-2-*phenylethylamides.*—2-Phenylethylamine, or its *p*-chloro-derivative (1 mol.), was dissolved in 50% acetone (20 parts), and the appropriate acid chloride (0·5 mol.) added in small portions with shaking and cooling. 2*N*-Sodium hydroxide (1·5 equivs.) was added and a further quantity of the acid chloride (0·7 mol.) added portionwise as before. The solution was diluted and filtered and the product crystallised from ethanol. The following were thus prepared (yields in parentheses): p-*nitrobenzo*-2-p-*chlorophenylethylamide* (72%), m. p. 148° (Found: N, 8·8; Cl, 11·3. $C_{15}H_{13}O_3N_2Cl$ requires N, 9·2; Cl, 11·7%); p-*chlorobenzo*-2-p-*chlorophenylethylamide* (74%), m. p. 147° (Found: N, 4·8; Cl, 23·8. $C_{15}H_{13}ONCl_2$ requires N, 4·8; Cl, 24·1%) [*p*-chlorobenzoic anhydride, m. p. 193°, was isolated as an insoluble by-product (Found: Cl, 23·6. Calc. for $C_{14}H_8O_3Cl_2$: Cl, 24·1%); cf. Frankland, Carter, and Adams, *J.*, 1912, **101**, 2479; Oden, *Chem. Zentr.*, 1919, III, 541]; p-*chlorobenzo*-2-*phenylethylamide* (78%), m. p. 134° (Found: N, 5·5; Cl, 13·6. $C_{15}H_{14}ONCl$ requires N, 5·4; Cl, 13·7%); and 4-*chloro*-3-*nitrobenzo*-2′-*phenylethylamide* (44%), m. p. 90° (Found: N, 9·3; Cl, 11·2. $C_{15}H_{13}O_3N_2Cl$ requires N, 9·2; Cl, 11·7%).

3 : 4-*Dihydroisoquinolines.*—The appropriate carboxyamide (1 part) and phosphoric oxide (5 parts) were refluxed in tetralin or toluene (25 parts) for 30—45 minutes. The product was decomposed with water, the aqueous layer separated and basified, and the precipitate crystallised or distilled. The following were thus prepared (yields in parentheses): 1-p-*chlorophenyl*-3 : 4-*dihydroisoquinoline* (90%), m. p. 77°, b. p. 160—165 (bath-temp.)/0·1 mm., white prisms from light petroleum (b. p. 80—100°) (Found: N, 5·7; Cl, 14·5. $C_{15}H_{12}NCl$ requires N, 5·8; Cl, 14·7%) [*hydrochloride*, white plates (from alcohol), m. p. 235—237° (Found: N, 4·8; Cl, 25·5. $C_{15}H_{13}NCl_2HCl$ requires N, 5·0; Cl, 25·6%)]; 7-*chloro*-1-p-*chlorophenyl*-3 : 4-*dihydroisoquinoline* (32%), m. p. 65—66°, b. p. 180—185° (bath-temp.)/0·05 mm., white prisms from light petroleum (b. p. 80—100°) (Found: N, 5·1; Cl, 25·2. $C_{15}H_{11}NCl_2$ requires N, 5·1; Cl, 25·7%) [*hydrochloride*, white plates (from alcohol), m. p. 237° (Found: N, 4·2; Cl, 34·1. $C_{15}H_{11}NCl_2HCl$ requires N, 4·5; Cl, 34·0%)]; 7-*chloro*-1-p-*nitrophenyl*-3 : 4-*dihydroisoquinoline* (47%), yellowish prisms (from ethanol), m. p. 148° (Found: C, 62·9; H, 4·0; N, 9·9. $C_{15}H_{11}O_2N_2Cl$ requires C, 62·8; H, 3·8; N, 9·8%), and 1-(4′-chloro-3′-nitrophenyl)-3 : 4-dihydro*iso*quinoline (48% as picrate), b. p. 200—210° (bath-temp.)/0·2 mm. [*picrate*, yellow prisms (from acetone–alcohol), m. p. 196° (sinters at 170°) (Found: N, 13·8; Cl, 7·1. $C_{15}H_{12}O_2N_2Cl$ requires N, 13·6; Cl, 6·9%)]. The base was regenerated from the picrate (3·6 g.) by shaking this salt with ether and saturated aqueous lithium hydroxide and was obtained as an *oil* (2·1 g.) which slowly solidified at 0° to a pale yellow solid, m. p. 62—63°.

7-*Nitro*-1-p-*chlorophenyl*-3 : 4-*dihydroisoquinoline.*—1-*p*-Chlorophenyl-3 : 4-dihydro*iso*quinoline (5 g.) was dissolved in nitric acid (*d* 1·4; 25 c.c.) and nitric acid (*d* 1·5; 50 c.c.) was added slowly with stirring and the solution set aside overnight. The solution was poured on ice and basified, and the precipitate filtered and crystallised from alcohol in pale yellow prisms (4·6 g., 77%), m. p. 137° (Found: C, 62·8; H, 3·8. $C_{15}H_{11}O_2N_2Cl$ requires C, 63·1; H, 4·1%). The *picrate* crystallised from alcohol in yellow needles, m. p. 160—170°, then solidifying, and remelting at 191° (Found: C, 49·1; H, 2·8. $C_{21}H_{14}O_9N_5Cl$ requires C, 48·9; H, 2·7%).

7-*Nitro*-1-(4′-*chloro*-3′-*nitrophenyl*)-3 : 4-*dihydroisoquinoline*.—(*A*) 1-*p*-Chlorophenyl-3 : 4-dihydroisoquinoline (1·2 g.) was dissolved in sulphuric acid (*d* 1·84; 4 c.c.) and a solution of potassium nitrate (1·5 g.) in sulphuric acid (*d* 1·84; 10 c.c.) was slowly added. The mixture was set aside overnight and then poured on ice and basified. The precipitated *isoquinoline* was filtered off and crystallised from alcohol in pale yellow needles (1·5 g., 91%), m. p. 108° (Found: C, 54·3; H, 3·0; N, 12·9. $C_{15}H_{10}O_4N_2Cl$ requires C, 54·3; H, 3·0; N, 12·7%). The *picrate* crystallised from acetone in yellow prisms, m. p. 214—215° (Found: N, 14·8; Cl, 6·2. $C_{21}H_{13}O_{11}N_5Cl$ requires N, 15·0; Cl, 6·3%).

(*B*) 7-Nitro-1-*p*-chlorophenyl-3 : 4-dihydroisoquinoline (0·7 g.) was nitrated by the method described in (*A*). The product crystallised from alcohol in pale yellow needles (1·6 g.), m. p. 108° showing no depression on admixture with the product from (*A*).

(*C*) 1-(4′-Chloro-3′-nitrophenyl)-3 : 4-dihydroisoquinoline (1 g.) was nitrated by the method described in (*A*). The product crystallised from alcohol in pale yellow needles, m. p. 108°, showing no depression on admixture with the product from (A). The picrate had m. p. 214—215° and showed no depression on admixture with the above salt.

7-*Amino*-1-p-*chlorophenyl*-3 : 4-*dihydroisoquinoline*.—7-Nitro-1-*p*-chlorophenyl-3 : 4-dihydroisoquinoline (5 g.) was refluxed in 5*N*-hydrochloric acid (120 c.c.) while iron dust (14 g.) was added portion-wise as rapidly as possible. The mixture was refluxed for 1 hour; crystals separated on cooling; these were redissolved and the solution was basified with aqueous ammonia and filtered. The residue was repeatedly extracted with hot alcohol, and the extract was evaporated to small bulk, diluted with water, extracted with ether, and dried. The ether was removed and the residue (2·25 g.) was crystallised from benzene–alcohol in pale yellow needles, m. p. 183° (Found: N, 11·0; Cl, 13·8. $C_{15}H_{13}N_2Cl$ requires N, 10·9; Cl, 13·9%). The *dihydrochloride* crystallised from alcohol in greenish prisms, m. p. 285° (Found: C, 54·6; H, 4·7; N, 8·6; Cl, 31·8. $C_{15}H_{13}N_2Cl,2HCl$ requires C, 54·6; H, 4·6; N, 8·5; Cl, 32·3%).

Proof of the Structure of 7-*Amino*-1-p-*chlorophenyl*-3 : 4-*dihydroisoquinoline*.—7-Amino-1-*p*-chlorophenyl-3 : 4-dihydroisoquinoline dihydrochloride (1·25 g.), dissolved in 2*N*-hydrochloric acid (5 c.c.), was diazotised at 0° with sodium nitrite (0·3 g.) in water (2 c.c.). After 15 minutes the solution was poured into a solution of cuprous chloride (1 g.) in hydrochloric acid (*d* 1·16; 20 c.c.) at 0°. Nitrogen was evolved rapidly and the solution was heated at 60° for 15 minutes. Excess of aqueous ammonia was added, the solution extracted with chloroform, and the extract washed with water and dried. The product was distilled [b. p. 180—190° (bath-temp.)/0·5 mm.] and the distillate converted into the hydrochloride (0·5 g.), m. p. 236—237°, which showed no depression on admixture with 7-chloro-1-*p*-chlorophenyl-3 : 4-dihydroisoquinoline hydrochloride, m. p. 237°. The regenerated base had m. p. 64—65° showing no depression on admixture with authentic material. The *picrate* crystallised from alcohol in yellow prisms, m. p. 152° (Found: N, 11·3; Cl, 13·9. $C_{21}H_{14}O_7N_4Cl_2$ requires N, 11·1; Cl, 14·1%).

Dehydrogenations.—The dihydro-base was intimately mixed with 10% of palladium black and heated in 1-g. portions for an appropriate time and temperature indicated in parentheses. The melt was powdered, extracted with hydrochloric acid, and filtered, and the filtrate was basified. The precipitate was crystallised from alcohol–acetone. Yields are indicated in parentheses. The following were thus obtained: 7-*Nitro*-1-p-*chlorophenylisoquinoline* (210—220°; 2 minutes), yellow needles (48%), m. p. 209° (Found: C, 63·7; H, 3·5; N, 9·8. $C_{15}H_9O_2N_2Cl$ requires C, 63·3; H, 3·2; N, 9·8%); 7-*chloro*-1-p-*nitrophenylisoquinoline* (210—215°; 10 minutes), yellow needles (44%), m. p. 176° (Found: C, 63·3; H, 3·3; N, 10·1. $C_{15}H_9O_2N_2Cl$ requires C, 63·3; H, 3·2; N, 9·8%), and 7-*nitro*-1-(4′-*chloro*-3′-*nitrophenyl*)*isoquinoline* (230°; 20 minutes), brown needles (48%), m. p. 221° (Found: N, 12·9; Cl, 10·5. $C_{15}H_8O_4N_3Cl$ requires N, 12·8; Cl, 10·8%).

Quaternisations.—The base was dissolved in nitrobenzene at 150°, methyl sulphate (2 mols.) added, and the mixture allowed to cool. The solution was diluted with ether and extracted with minimal amounts of water, and the methiodide precipitated by addition of excess of potassium iodide. Thus were obtained 7-*nitro*-1-p-*chlorophenylisoquinoline methiodide*, small brown plates, m. p. 228—229° (decomp.) (90%) (Found: N, 6·7; I, 29·8. $C_{16}H_{12}O_2N_2ClI$ requires N, 6·6; I, 29·8%), 7-*chloro*-1-p-*nitrophenylisoquinoline methiodide*, orange needles (82%), m. p. 235—236° (decomp.) (Found: N, 6·8. $C_{16}H_{12}O_2N_2ClI$ requires N, 6·6%), and 1-p-*nitrophenylisoquinoline methiodide*, yellow prisms (79%), m. p. 244° (Found: N, 7·1; I, 32·7. $C_{16}H_{13}O_2N_2I$ requires N, 7·1; I, 32·4%).

Reductions.—(A) *Nitro-bases*. The nitro-base (1 part) was dissolved in boiling 5*N*-hydrochloric acid (25 parts), iron dust (3 parts) added as rapidly as possible, and the mixture refluxed for 1 hour. The hot solution was filtered and the filtrate basified with excess of aqueous ammonia and filtered. The residue was extracted with hot alcohol, and the extract evaporated to small bulk and diluted with water. The base was taken up in ether and precipitated as the dihydrochloride which was crystallised from methanol. Thus were obtained 7-*chloro*-1-p-*aminophenylisoquinoline dihydrochloride*, red needles (78%), m. p. indefinite (softens at 250°, resolidifies and remelts at 288—290°) (Found: C, 52·9; H, 4·6; N, 8·2; loss at 100°/1 mm., 4·9. $C_{15}H_{11}N_2Cl,2HCl,H_2O$ requires C, 52·1; H, 4·3; N, 8·1; loss, 5·2%) [the *base* crystallised from light petroleum (b. p. 80—100°) in pale yellow needles, m. p. 112—113° (Found: C, 70·1; H, 4·5; N, 11·3. $C_{15}H_{11}N_2Cl$ requires C, 70·7; H, 4·3; N, 11·0%)], and 7-*amino*-1-p-*chlorophenylisoquinoline dihydrochloride*, sandy prisms (71%), m. p. 305° (Found: C, 54·3; H, 4·0; N, 8·9. $C_{15}H_{11}N_2Cl,2HCl$ requires C, 55·0; H, 4·0; N, 8·5%).

(B) *Quaternary salts*. The nitro-derivative (1 part) was dissolved in hot water (60 parts) containing 2*N*-hydrochloric acid (2 parts) and was added to a stirred boiling suspension of reduced iron (1 part) in water (60 parts). The mixture was refluxed for 1·5 hours and then filtered and the iron precipitated by a slight excess of aqueous ammonia. The filtrate was evaporated to small bulk and filtered, and the methiodide precipitated by addition of solid potassium iodide and crystallised from hot water. Thus were obtained 7-*amino*-1-p-*chlorophenylisoquinoline methiodide*, yellow needles (87%), m. p. 262° (Found: N, 7·2; I, 31·9. $C_{16}H_{14}N_2ClI$ requires N, 7·1; I, 32·0%), 7-*chloro*-1-p-*aminophenylisoquinoline methiodide*, orange needles (77%) of indefinite m. p. (sinters at 143—145° and melts *ca.* 155°) (Found: C, 46·6; H, 4·0; N, 7·1; loss at 100°/10 mm., 3·3. $C_{16}H_{14}N_2ClI,H_2O$ requires C, 46·3; H, 3·9; N, 6·8; loss, 4·3%), and 1-p-*aminophenylisoquinoline methiodide*, yellow prisms (71%), m. p. 206° (Found: N, 7·8; I, 35·3. $C_{16}H_{15}N_2I$ requires N, 7·7; I, 35·1%).

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372. *Hydrogenation of Diphenylene Oxide and 2 : 2′-Dihydroxydiphenyl.*

By J. IDRIS JONES and A. S. LINDSEY.

The products obtained by pressure hydrogenation of diphenylene oxide and 2 : 2′-dihydroxydiphenyl over Raney nickel are described. The existence of a hexahydrodiphenylene oxide of unknown stereochemical configuration has been confirmed. The ultra-violet absorption spectra of diphenylene oxide, tetra- and hexa-hydrodiphenylene oxide, coumarone, and coumaran have been measured and are compared.

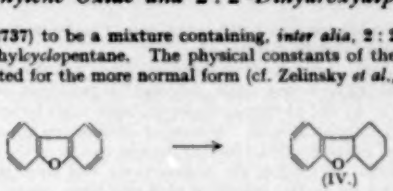
A SURVEY of the literature showed that some confusion existed over the preparation and homogeneity of the hydrogenation products of diphenylene oxide and 2 : 2′-dihydroxydiphenyl, and that the independent existence of one of these products, namely hexahydrodiphenylene oxide, was doubtful. The present work has sought to clarify the position by a re-examination of the preparative methods given in the literature and by the preparation of pure samples of some of the materials involved and characterisation of them by means of their ultra-violet absorption spectra.

Cullinane and Padfield (*J.*, 1935, 1131), for example, claim to have prepared tetrahydrodiphenylene oxide by controlled hydrogenation of diphenylene oxide over platinum black, but give no proof of the homogeneity of their product. Again Fieser *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 2966) state that hexahydrodiphenylene oxide has been prepared as an intermediate, by reduction of 2 : 2′-dihydroxydiphenyl (von Braun, *Ber.*, 1922, **55**, 3763), but Gilman, Smith, and Chaney (*J. Amer. Chem. Soc.*, 1935, **57**, 2095) had shown earlier that the derivatives obtained by von Braun (*loc. cit.*) from the reduction products, and regarded by him as derived from hexahydrodiphenylene oxide, corresponded to the tetrahydrodiphenylene oxide derivatives. Gilman *et al.* (*loc. cit.*) were also unable to confirm the claim of Ebel (*Helv. Chim. Acta*, 1929, **12**, 11) to have reduced the tetra- to the hexa-hydrodiphenylene oxide. Stenger (G.P. 566,782/1930) obtained perhydrodiphenylene oxide by hydrogenation of diphenylene oxide over a nickel catalyst but did not mention any other products of the reaction. On the other hand, Hall and Cawley (*J. Soc. Chem. Ind.*, 1939, **58**, 7), by hydrogenation-cracking of diphenylene oxide over molybdenum oxide and sulphide catalysts at high temperatures, obtained as an initial product *o-cyclo*hexylphenol, which became further hydrogenated and broken down to yield a number of products, amongst which was di*cyclo*hexyl.

In the present work diphenylene oxide has been subjected to both exhaustive and controlled hydrogenation over Raney nickel at a high temperature and pressure. In the former instance perhydrodiphenylene oxide (I) was obtained as the main product; cleavage of the furan ring

also occurred to give di*cyclo*hexyl (III) and the *cis*- and *trans*-isomers of 2-*cyclo*hexyl*cyclo*hexanol (II). Identification of the last-named isomers was confirmed by preparation of their phthalates and phenylurethane derivatives; and in both cases chromic acid oxidation of the isomers yielded *cyclo*hexyl*cyclo*hexanone which was directly compared with a synthetic specimen. The identity of the di*cyclo*hexyl obtained during hydrogenolysis was confirmed by comparing its infra-red absorption spectrum with that of an authentic sample of di*cyclo*hexyl obtained by dehydration of *cis-cyclo*hexyl*cyclo*hexanol followed by hydrogenation. These spectra were substantially indentical. Various Sachse–Mohr stereoisomers of di*cyclo*hexyl are mentioned in the literature. Hückel and Neunhoeffer (*Annalen*, 1930, **477**, 106), however, were unable to confirm the preparation of three forms of this compound by dehydration of *cis*- and *trans-cyclo*hexyl*cyclo*hexanols and hydrogenation of the products (Schrauth and Görig, *Ber.*, 1923, **56**, 1900), and concluded that such isomers do not exist. The *trans-trans*-isomer of Levina *et al.* (*J. Gen. Chem., Russia*, 1937, **7**, 341) was found by Orchin and Feldman (*J. Amer.*

Chem. Soc., 1946, **68**, 2737) to be a mixture containing, *inter alia*, 2 : 2'-dimethyldi*cyclo*pentyl and 1-*cyclo*hexyl-2-methyl*cyclo*pentane. The physical constants of the product now obtained are close to those reported for the more normal form (cf. Zelinsky *et al.*, *Chem. Zentr.*, 1933, II, 1673).

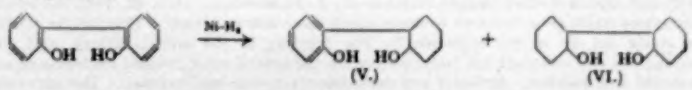


(IV.)

Controlled hydrogenation of diphenylene oxide so that three moles of hydrogen were absorbed yielded hexahydrodiphenylene oxide (IV) as the chief product. This material could be readily dehydrogenated to diphenylene oxide by heating it in contact with platinised charcoal, and gave on oxidation with chromic acid at room temperature δ-*o*-hydroxybenzoylvaleric acid. The same acid was also obtained by chromic acid oxidation of tetrahydrodiphenylene oxide and it is likely that the hexahydrodiphenylene oxide used by Fieser *et al.* (*loc. cit.*) for the preparation of this acid was a mixture of both the tetra- and the hexahydro-oxides.

The methods reported by Ebel and by von Braun (*locc. cit.*) for the preparation of hexahydrodiphenylene oxide were investigated. Tetrahydrodiphenylene oxide took up one mole of hydrogen slowly in alcoholic solution, and much more rapidly in glacial acetic acid, in the presence of platinum or palladium black at room temperature, to give a product which chemical analysis indicated to be hexahydrodiphenylene oxide. The ultra-violet absorption spectrum of this product, however, showed it to be a mixture of approximately 75% of tetra- and 25% of per-hydrodiphenylene oxide only. No break in the rate of hydrogenation curve was observed in these experiments and it would appear that, under the conditions mentioned, hydrogenation of both rings occurred before the molecule was desorbed from the catalyst. Smith *et al.* (*J. Amer. Chem. Soc.*, 1949, **71**, 3772) have shown that for dinuclear compounds, such as diphenyl, hydrogenation of one ring initially occurred, followed by desorption of the molecule from the catalyst, and in such cases, when the hydrogenation was halted at a half-way stage, the bulk of the product existed as the hexahydro-compound. On the other hand, addition of three moles of hydrogen to diphenylene oxide under similar conditions gave a mixture of perhydro- and unchanged diphenylene oxide (Smith and Fuzek, *J. Amer. Chem. Soc.*, 1949, **71**, 415) and it is probable that the tetrahydrodiphenylene oxide prepared by Cullinane and Padfield (*loc. cit.*) was chiefly unchanged diphenylene oxide.

When 2 : 2'-dihydroxydiphenyl was hydrogenated over Raney nickel so that between two and three moles of hydrogen were absorbed, and the products were carefully fractionated through a Stedman-type column, two main liquid products together with 60% of solid residue were obtained. Ultra-violet absorption analysis of the lower-boiling fraction showed it to be a crude specimen of hexahydrodiphenylene oxide admixed with some tetra- and per-hydrodiphenylene oxides. The higher-boiling fraction was identified as tetrahydrodiphenylene oxide by means of its picrate and physical constants. From the solid residue *o*-2-hydroxy*cyclo*hexylphenol (V) and 2 : 2'-dihydroxydi*cyclo*hexyl (VI) were isolated by fractional crystallisation. Neither of the two compounds appears to have been previously characterised. The "dodecahydro-*o*-*o*'-diphenol" mentioned by Schwenk and Priewe (G.P. 602,837/1934) has a much lower melting point (143—145°) than the compound isolated by us; it may be an impure sample of the same compound or is possibly another stereoisomer. The perhydrodiphenol readily formed a bisphenylurethane and a bis-3 : 5-dinitrobenzoate, and from its mode of formation is most likely to be (VI). The *o*-2-hydroxy*cyclo*hexylphenol would only yield a mono-phenylurethane when treated with phenyl *iso*cyanate under the normal reaction conditions; this derivative still possessed a free phenolic group and could be readily coupled with a diazonium salt. Dehydration of the hexahydro-phenol by means of fused potassium hydrogen sulphate removed the alcoholic hydroxyl group, giving one of the isomeric *cyclo*hexenylphenols. The hexahydro-phenol most probably corresponds to the half-hydrogenated form of 2 : 2'-dihydroxydiphenyl (V).



(V.) (VI.)

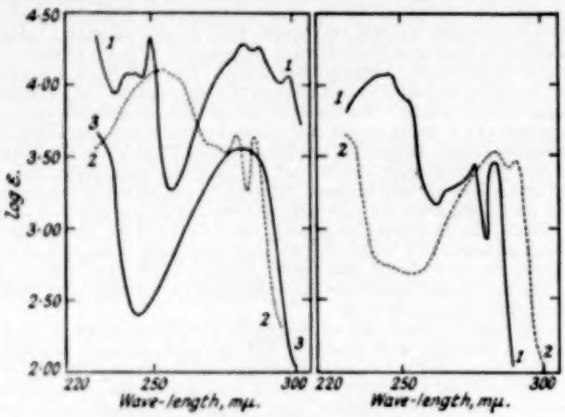
Investigation of the stereochemical configuration of these two compounds was not carried out, but it is interesting that quantitative hydrogenation of 2 : 2'-dihydroxydiphenyl over

Adams's catalyst at room temperature yields a mixture of perhydrodiphenylene oxide and the 2 : 2'-dihydroxydi*cyclo*hexyl already mentioned.

An independent synthesis of hexahydrodiphenylene oxide was also attempted by preparation of 1 : 4 : 10 : 11-tetrahydrodiphenylene oxide, followed by reduction of the 2 : 3-double bond. It was hoped to prepare 1 : 4 : 10 : 11-tetrahydrodiphenylene oxide by condensation of butadiene with coumarone or with coumarilic acid. A number of experiments at various temperatures and with various times of heating failed, however, to lead to any of the desired product.

It was considered useful to confirm the homogeneity and structure of the hexahydrodiphenylene oxide, obtained by partial reduction of diphenylene oxide, by measurement of its ultra-violet absorption spectrum. Some of the material was therefore purified by adsorption on to a dry column of alumina, followed by desorption with absolute alcohol (cf. *Analyt. Chem.*, 1947, **19**, 992), giving 60% of a pure material of constant refractive index. The ultra-violet absorption spectrum of this material (Fig. 1, curve 3) was closely similar to that of the starting material which lent some support to its homogeneity. For comparison the ultra-violet absorption spectra of pure samples of diphenylene oxide, tetrahydrodiphenylene oxide (Fig. 1,

FIG. 1. FIG. 2.



Absorption spectra, in cyclo*hexane.*

FIG. 1.—1, *Diphenylene oxide.* 2, *Tetrahydrodiphenylene oxide.* 3, *Hexahydrodiphenylene oxide.*
FIG. 2.—1, *Coumarone.* 2, *Coumaran.*

curves 1 and 2 respectively), coumarone, and coumaran (Fig. 2, curves 1 and 2 respectively) were also measured. F. Williams (*Nature*, 1948, **162**, 925) has shown that the melting point of diphenylene oxide is no criterion of its purity and, in view of the difficulty of obtaining, from coal tar, a pure specimen suitable for spectroscopic work, preparation by a synthetic route was obviously desirable. This was accomplished by dehydrogenating tetrahydrodiphenylene oxide, synthesised by Ebel's method (*loc. cit.*), by means of *N*-bromosuccinimide (cf. Barnes, *J. Amer. Chem. Soc.*, 1948, **70**, 145). The diphenylene oxide so obtained was then purified by crystallisation followed by chromatography and sublimation. Pure coumarone was prepared by decarboxylation of coumarilic acid; and coumaran by hydrogenation of coumarone over Adams's catalyst at room temperature.

In comparison with the spectra of diphenyl (O'Shaughnessy and Rodebush, *ibid.*, 1940, **62**, 2906) and diphenyl ether (Mayer-Pitsch *et al.*, *Z. Elektrochem.*, 1943, **49**, 368), the spectrum of diphenylene oxide (Fig. 1, curve 1) shows much more fine structure. This can be attributed to the strain set up in the molecule by the bonding in the *ortho*-positions, and similar enhancement of fine structure has been observed in the case of other bridged nuclear compounds (cf. diphenyl and fluorene; diphenyl and carbazole; *o*-xylene and indane). The curve shown here for diphenylene oxide in *cyclo*hexane agrees very closely with that recently published by the U.S. Bureau of Mines (Tech. Paper 708) for a synthetic sample in 95% ethanol.

Some of the fine structure is eliminated, however, when hydrogen is added at the 1 : 2 : 3 : 4-positions of diphenylene oxide (Fig. 1, curve 2), and the bands at 242, 245, and 250 mμ. are replaced by a broad band having a maximum at 253 mμ. At the same time the 282-, 287-, and 298-mμ. bands are shifted towards the shorter wave-band of the spectrum, as might be expected for a system containing a smaller number of conjugated double bonds (Hausser and Kuhn, *Z. physikal. Chem.*, 1935, **29**, *B*, 363). Comparison of the diphenylene oxide spectrum with the ultra-violet absorption spectrum of coumarone (Fig. 2, curve 1) shows both the curves to be very similar in general shape and position of absorption maxima. Both molecules resemble indene in containing the $C_6H_4{\cdot}C\overset{|}{\underset{|}{C}}$ chromophore, and it is interesting that the positions of the absorption bands are in agreement with Morton and de Gouveia's suggestion (*J.*, 1934, 915) that the C_6H_4· part of such a chromophore would give rise to bands in the 270—290-mμ. wave-length region and the ethylenic bond to a band about 250 mμ. This is shown in the table below.

Maximum absorption bands.

Diphenylene oxide.		Tetrahydrodi-phenylene oxide.		Coumarone.		Indene.*		Hexahydrodi-phenylene oxide.		Coumaran.		Indane.*	
λ (max.), mμ.	log ε	λ (max.), mμ.	log ε	λ (max.), mμ.	log ε	λ (max.), mμ.	log ε	λ (max.), mμ.	log ε	λ (max.), mμ.	log ε	λ (max.), mμ.	log ε
242	4·09	—	—	—	—	—	—	—	—	—	—	—	—
245	4·09	253	4·11	245	4·08	246	4·00	—	—	—	—	—	—
249·5	4·32	—	—	—	—	—	—	—	—	—	—	—	—
281·5	4·29	272	3·58	—	—	273	2·94	—	—	—	—	260	3·00
287	4·28	279	3·66	275	3·45	280	2·90	280	3·56	282	3·52	267	3·16
298	4·06	286	3·65	282	3·48	288	2·73	—	—	289	3·48	274	3·25
—	—	—	—	—	—	291·5	2·21	—	—	—	—	—	—

* Values taken from Morton and de Gouveia, *J.*, 1934, 915.

Addition of hydrogen to the 10 : 11-positions to give hexahydrodiphenylene oxide (IV) causes elimination of the 253-mμ. band of tetrahydrodiphenylene oxide and replaces the three peaks between 270—290 mμ. by a broad band with a maximum at 280 mμ. It might be expected that saturation of the 10 : 11-double bond would cause a much greater shift of $\lambda_{max.}$ away from the visible region, but comparison of the spectra of coumarone and coumaran, where a similar saturation of the 2 : 3-double bond has been carried out, shows that for this type of molecule a shift of the maxima occurs towards the visible region of the spectrum. This anomalous shift appears to be associated with the presence of a cyclic oxygen atom in the molecule. Examination of the spectra of indene and indane (*J.*, 1934, 915) shows that saturation of the 1 : 2-double bond in this case causes the more usual shift of the absorption bands away from the visible, and a similar effect is observable on comparison of the spectra of 1 : 2 : 3 : 4-tetrahydrophenanthrene and 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (Askew, *J.*, 1935, 512).

The close similarity of the spectra of coumaran and hexahydrodiphenylene oxide strongly supports the structure (IV) already suggested from dehydrogenation and oxidation experiments, and there can be little doubt that hexahydrodiphenylene oxide definitely exists as a stable chemical entity. The stereochemical configuration of the material prepared by us has, however, not been investigated, but it would appear to differ from that of the hexahydrodiphenylene oxide described by Cornforth, Hughes, and Lions (*J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 323) who obtained it by pyrolysis of phenyl *cyclo*hexenyl ether.

Experimental.

Exhaustive Hydrogenation of Diphenylene Oxide.—Diphenylene oxide (1 kg.) in absolute alcohol (750 ml.) was exhaustively hydrogenated over Raney nickel (60 g.) in a 2-litre stainless-steel autoclave at 190°/200 atm. during 23 hours. The liquid products (1078 g.) were fractionated through a Stedman column (equivalent to 50 theoretical plates), at 20 mm., giving four main fractions :

Fraction 1 (34 g.), b. p. 116—118°/20 mm., n_D^{20} 1·4800, m. p. 4·5° (Found : C, 86·65; H, 13·3. Calc. for $C_{12}H_{22}$: C, 86·7; H, 13·3%), was shown to be di*cyclo*hexyl by comparison of its infra-red absorption spectrum with that of di*cyclo*hexyl prepared by dehydration of *cis-cyclo*hexyl*cyclo*hexanol, followed by hydrogenation over palladium black in acetic acid solution at room temperature.

Fraction 2 (365 g.), b. p. 134—137°/20 mm., n_D^{20} 1·5000 (Found : C, 80·2; H, 11·0. Calc. for $C_{12}H_{20}O$: C, 80·0; H, 11·1%), agreed in its physical and chemical properties with perhydrodiphenylene oxide. Gilman *et al.* (*J. Amer. Chem. Soc.*, 1935, **57**, 2095) give b. p. 258—259°/740 mm., n_D^{25} 1·5023. Smith and Fuzek (*ibid.*, 1949, **71**, 415) give b. p. 162°/45 mm., n_D^{20} 1·4990.

Fraction 3 (205 g.), b. p. 149—151°/20 mm., solidified when kept and on recrystallisation from light petroleum had m. p. 61° (Found : C, 79·05; H, 11·8. Calc. for $C_{12}H_{20}O$: C, 79·05; H, 12·2%). This

material readily formed a phthalate, m. p. 115°, and a phenylurethane, m. p. 153°. Hückel *et al.* (*Annalen*, 1930, **477**, 99) give *cis-o-cyclo*hexylcyclohexanol, m. p. 63° (phenylurethane, m. p. 153°). Vavon (*Bull. Soc. chim.*, 1926, **39**, 1138) reports two forms of the phthalate, *viz.*, m. p. 112—113° and 126—127°.

Fraction 4 (272 g.), b. p. 151—153°/20 mm., also solidified after distillation. Repeated recrystallisation from light petroleum gave a material, m. p. 52—53° (Found: C, 79·1; H, 11·9. Calc. for $C_{12}H_{22}O$: C, 79·05; H, 12·2%). The derived phenylurethane, after repeated recrystallisation from light petroleum (b. p. 80—100°), had m. p. 133—134° alone and admixed with the phenylurethane (m. p. 133—134°) of authentic *trans-o-cyclo*hexylcyclohexanol (prepared by reduction of *cyclo*hexylcyclohexanone; Hückel *et al.*, *loc. cit.*). Vavon (*loc. cit.*) gives phenylurethane, m. p. 132°; Hückel *et al.* (*loc. cit.*) give 136°.

Chromic acid oxidation of the last two fractions at room temperature yielded the same *o-cyclo*hexylcyclohexanone. Authentic *o-cyclo*hexylcyclohexanone, prepared according to Hückel *et al.* (*loc. cit.*), gave two products on treatment with alcoholic 2 : 4-dinitrophenylhydrazine: one, m. p. 120—121°, as orange flakes, easily soluble in alcohol, and a second, m. p. 176·5—177°, as orange needles (from alcohol–chloroform), sparingly soluble in alcohol. These two derivatives presumably correspond to the *syn*- and *anti*-forms. For ease in purification, the less soluble derivative melting at 176·5—177° was used, and admixture with the corresponding 2 : 4-dinitrophenylhydrazones prepared from the chromic acid oxidation products (both melting at 176—177°) led to no depression in melting point.

Partial Hydrogenation of Diphenylene Oxide.—Diphenylene oxide (1 kg.) in alcohol (750 ml.) was hydrogenated over Raney nickel at 200°/200 atm. until approximately 3 moles of hydrogen had been taken up. The crude product was steam-distilled, and the liquid products (483 g.) were fractionated through a Stedman-type column at 20 mm., yielding 50% of unchanged diphenylene oxide in the still and a main liquid fraction (36%), b. p. 140—142°/20 mm., n_D^{20} 1·5491, namely, *hexahydrodiphenylene oxide*, a colourless mobile liquid, with a pleasant aromatic smell, which did not yield a picrate (Found: C, 82·8; H, 7·9. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%). A small fraction, b. p. 134—136°/20 mm., collected in the above distillation was also examined (see below).

Purification of the hexahydrodiphenylene oxide. 4 Ml. of the fraction, b. p. 140—142°/20 mm., were adsorbed on a column of dry activated alumina (33" × ½" at top, tapering to ¼" at base) and subsequently desorbed with 20 ml. of absolute alcohol under slight air pressure at the top of the column (1—2 lbs./sq. in.), 0·2-ml. fractions being collected. The middle fractions (corresponding to 60% of the starting material) had a constant n_D^{20} = 1·5515.

Dehydrogenation of hexahydrodiphenylene oxide. The fraction, b. p. 140—142°/20 mm. (2·0 g.), was heated at 270—290° for 5 hours with platinised charcoal (0·2 g.). A quantitative yield of a white solid, m. p. 74—76° after one crystallisation from hot alcohol, was obtained, infra-red absorption analysis of this material showing it to be substantially pure diphenylene oxide. Repeated recrystallisation from alcohol gave m. p. 81·0—82·0° undepressed when mixed with authentic diphenylene oxide (m. p. 82—83°). Likewise a mixed m. p. of the derived picrate with the same derivative of diphenylene oxide (m. p. 96—97°) showed no depression.

Chromic acid oxidation of tetra- and hexa-hydrodiphenylene oxide. 5·0-G. quantities of both the hexahydrodiphenylene oxide and the synthetic tetrahydrodiphenylene oxide (see below) were separately oxidised by keeping them in contact with chromic acid at room temperature for 24 hours. Both compounds yielded the same δ-o-hydroxybenzoylvaleric acid, m. p. 93—94° (Found: C, 64·7; H, 6·25. Calc. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35%).

Examination of the fraction, b. p. 134—136°/20 mm. Dehydrogenation of this fraction over platinised charcoal yielded a mixture of diphenylene oxide and fluorene. Infra-red absorption analysis of the diphenylene oxide used in these experiments showed it to contain a small amount of fluorene. Hydrogenation followed by fractionation had obviously concentrated the fluorene, in a hydrogenated form, in the 134—136°/20 mm. fraction. No further examination of the fraction was carried out.

Partial Hydrogenation of 2 : 2′-Dihydroxydiphenyl.—2 : 2′-Dihydroxydiphenyl (200 g.) in alcohol was hydrogenated over Raney nickel (20 g.) at 200°/120 atm. until approx. 2 moles of hydrogen had been absorbed. The dark brown, rather viscous product (193 g.) was distilled through a Stedman-type column, yielding two main liquid fractions, b. p. 142—146°/20 mm., n_D^{20} 1·5461 (Found: C, 82·8; H, 8·45. Calc. for $C_{12}H_{14}O$: C, 82·7; H, 8·1%) (8% yield), and 154—158°/20 mm., n_D^{20} 1·5695 (23% yield), and leaving a solid residue (60%) in the still.

Attempted purification of the lower-boiling fraction by adsorption on a column of dry alumina was not completely successful, since, although the refractive index of the material was raised considerably, the ultra-violet absorption spectrum indicated that this purified material contained only 80% of hexahydrodiphenylene oxide, the other 20% apparently being a mixture of tetra- and per-hydrodiphenylene oxides.

The higher-boiling fraction readily yielded a picrate, m. p. 98° (from alcohol), which gave no depression on admixture with the picrate of authentic tetrahydrodiphenylene oxide (m. p. 98°).

Investigation of the solid residue. In another experiment the total reaction product was steam-distilled, and the non-volatile portion worked up in the usual manner and finally distilled at 9 mm. pressure. After a small mobile fore-fraction, the bulk distilled as a viscous syrup, b. p. 194—200°/9 mm., which solidified on cooling and on fractional crystallisation from light petroleum (b. p. 60—80°) yielded a small amount of colourless hexagonal prisms, m. p. 180—181° (Found: C, 72·4; H, 11·2. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%) and a much larger quantity of material as colourless plates, m. p. 115—116° (Found: C, 74·9; H, 8·5. $C_{12}H_{12}O_2$ requires C, 75·0; H, 8·4%).

The former compound, 2 : 2′-*dihydroxy*dicyclo*hexyl*, m. p. 180—181°, readily formed a *bisphenylurethane*, m. p. 273° (from alcohol) (Found: C, 71·2; H, 7·4; N, 6·4. $C_{38}H_{38}O_4N_2$ requires C, 71·55; H, 7·4; N, 6·4%), and a *bis*-3 : 5-*dinitrobenzoate*, m. p. 292° (crystallised from benzene–nitrobenzene) (Found: C, 53·5; H, 4·7; N, 10·0. $C_{26}H_{18}O_{12}N_4$ requires C, 53·2; H, 4·5; N, 9·6%).

The latter compound, o-2-*hydroxy*cyclo*hexyl*phenol, m. p. 115—116°, gave an olive-green colour in aqueous-alcoholic solution with neutral ferric chloride, and readily coupled with diazotised *p*-nitroaniline.

It yielded a *mono-phenylurethane*, m. p. 172° (Found : C, 73·3; H, 6·8; N, 4·5. $C_{19}H_{21}O_3N$ requires C, 73·3; H, 7·0; N, 4·5%), by reaction with the alcoholic hydroxyl group. A *O*-carboxymethyl derivative, m. p. 132° (prepared as described by Koelsch, *J. Amer. Chem. Soc.*, 1931, **53**, 304), was also obtained.

Hydrogenation of 2 : 2'-*dihydroxydiphenyl over platinum.* 2 : 2'-Dihydroxydiphenyl, m. p. 109—111° (1·0 g.), in glacial acetic acid (25 ml.), was hydrogenated at room temperature and pressure over Adams's catalyst (0·2 g.). (Hydrogen absorption = 780 c.c. Theor. for complete saturation = 780 c.c.) The hydrogenated product was treated with dilute sodium hydroxide, and the insoluble oil removed by ether-extraction and subsequently distilled at reduced pressure (some decomposition occurring), to yield a small amount of a colourless liquid, n_D^{25} 1·4989 (Found : C, 79·8; H, 11·3. Calc. for $C_{12}H_{22}O$: C, 79·9; H, 11·2%), considered to be perhydrodiphenylene oxide. The residue left in the flask treated with phenyl *iso*cyanate yielded white feathery crystals (from alcohol), m. p. 272—273° (alone or admixed with the bisphenylurethane of 2 : 2'-dihydroxydi*cyclo*hexyl described above).

Hydrogenation of tetrahydrodiphenylene oxide over platinum. Pure tetrahydrodiphenylene oxide (0·3 g.), prepared as described below, was quantitatively hydrogenated at room temperature and pressure in the presence of glacial acetic acid and Adams's catalyst (0·1 g.), in an apparatus similar to that described by Jackson and Jones (*J.*, 1936, 895) until 42·5 c.c. of hydrogen had been absorbed (theor. for conversion into hexahydrodiphenylene oxide = 41·9 c.c.). Absorption took place rapidly during 20 minutes, but no break in the rate of absorption was observed at the end of this time. Measurement of the ultra-violet absorption spectrum of the recovered product, n_D^{25} 1·5568 (Found : C, 82·7; H, 8·3. Calc. for $C_{12}H_{14}O$: C, 82·7; H, 8·1%), showed it to contain approximately 75% of unchanged tetrahydrodiphenylene oxide and 25% of perhydrodiphenylene oxide.

Preparation of Pure Tetrahydrodiphenylene Oxide.—Tetrahydrodiphenylene oxide, synthesised by Ebel's method (*Helv. Chim. Acta*, 1929, **12**, 11), was purified by regeneration from its picrate, m. p. 98°, and possessed the following physical constants : b. p. 154—156°/20 mm., n_D^{25} 1·5787 (Found : C, 83·6; H, 7·2. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 7·0%).

Preparation of Pure Diphenylene Oxide.—To tetrahydrodiphenylene oxide (2·5 g.) in dry carbon tetrachloride (35 ml.) were added *N*-bromosuccinimide (5·2 g.) and benzoyl peroxide (0·1 g.), and the mixture was gently refluxed for 1½ hours. Sodium acetate (5 g.) and glacial acetic acid (2 ml.) were then added and the whole was refluxed for a further half hour. The reaction mixture was poured on ice–sodium hydroxide (solid). The product, isolated in ether, was distilled at 2 mm., giving 1·8 g. (72%) of a slightly yellow solid of m. p. about 79°. After 2 recrystallisations from alcohol, chromatography [in light petroleum (b. p. 40—60°)] on alumina, recrystallisation from alcohol, and sublimation under reduced pressure, the diphenylene oxide was obtained as lustrous white flakes, m. p. 82·0—83·0° (Found : C, 85·5; H, 4·65. Calc. for $C_{12}H_8O$: C, 85·7; H, 4·8%) (F. Williams, *loc. cit.*, gives the m. p. of pure diphenylene oxide as 82·8—83·0°).

Preparation of Pure Coumarone.—Recrystallised coumarilic acid (*Org. Synth.*, **24**, 33), m. p. 192°, was dry distilled with soda-lime. Ether-extraction of the oil–water distillate, followed by distillation of the dried product, yielded coumarone, n_D^{25} 1·5666 (*J. Inst. Physics*, 1947, **33**, 687 : n_D^{25} 1·5663).

Preparation of Pure Coumaran.—Coumarone, b. p. 171°, in glacial acetic acid was hydrogenated over Adams's catalyst at room temperature and pressure until 1 g.-mol. of hydrogen had been absorbed. The recovered product, purified by conversion into the picrate, had constant m. p. 75—76° (pre-heated bath) after 3 recrystallisations from alcohol. Regeneration from the picrate followed by distillation yielded coumaran, n_D^{25} 1·5479 (Found : C, 79·7; H, 6·6. Calc. for C_8H_8O : C, 80·0; H, 6·7%) (Rindfuss, *J. Amer. Chem. Soc.*, 1919, 669, gives n_D^{25} = 1·543).

From the higher refractive index and the slight inflexion in the ultra-violet absorption curve at 245 mμ. it would appear that the sample still contained a small amount of coumarone. Owing to the small amount available further purification was not undertaken.

Measurement of Ultra-violet Absorption Spectra.—The ultra-violet absorption spectra were measured with a Beckman Quartz Spectrophotometer, using approx. 10^{-4}M-solutions in *cyclo*hexane.

Analyses were carried out by Dr. Weiler and Dr. Strauss, Oxford.

In the temporary absence of the senior author (J. I. J.), Dr. N. J. Cartwright supervised the concluding stages of the work and we are also indebted to him for valuable assistance in the preparation of the manuscript. We thank Mr. W. Kynaston for measuring the ultra-violet absorption spectra and Dr. E. F. G. Herington for many helpful discussions on their interpretation. Mr. J. Hales kindly performed the infra-red absorption analyses.

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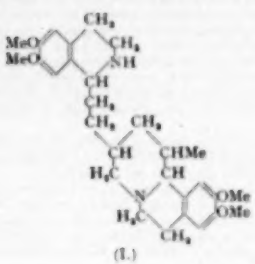
373. *Structure and Amœbicidal Activity. Part I. Aliphatic Diamines.*

By D. Muriel Hall, Sardar Mahboob, and E. E. Turner.

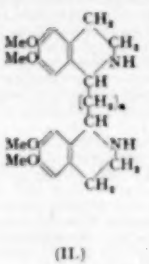
Fourteen aliphatic diamines of the type $NH_2{\cdot}CHR{\cdot}[CH_2]_n{\cdot}CHR{\cdot}NH_2$ have been synthesised as their dihydrochlorides. Three of them with $n = 3$ and one with $n = 4$ are effective against *Entamœba histolytica* at a concentration of 1 in 10^6. (Emetine is effective at a concentration of 1 in 5×10^6.)

Attempts to dissect out that portion of the emetine molecule which might be responsible for the amœbicidal action of the alkaloid have so far met with little success. Thus, Child and Pyman (*J.*, 1929, 2010) basing their ideas on Pyman's emetine formula (I) (*J.*, 1927, 1067) prepared a series of compounds of the type (II), or closely related thereto, with $n = 4$, 5, or 8. None of the substances examined was active against *Entamœba histolytica* at dilutions of 1 in 5000, whereas emetine is effective at 1 in 500,000.

Later, however, Pyman (*Rep. Brit. Ass.*, 1937, **107**, 57) reported some amœbicidal activity on the part of 1 : 10-bisdiamylaminododecane. Goodson, Gorvin, Goss, Kirby, Lock, Neal, Sharp, and Solomon (*Brit. J. Pharmacol.*, 1948, **3**, 49) examined a considerable series of compounds, including some of the types $[3:4:1\text{-}(OMe)_2C_6H_3{\cdot}NH]_2{>}[CH_2]_n$ and $(n\text{-}C_6H_{13}{\cdot}NH)_2{>}[CH_2]_n$ and also the one primary diamine $NH_2{\cdot}[CH_2]_{10}{\cdot}NH_2$.



(I.)



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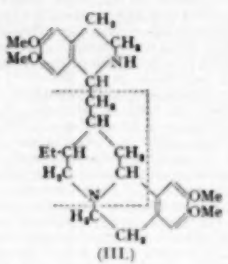

(III.)

The correction of the formula for emetine to (III) (Robinson, *Nature*, 1948, **162**, 524; Pailer and Porschinski, *Monatsh.*, 1949, **80**, 94; Battersby, Openshaw, and Wood, *Experientia*, 1949, **5**, 114; Battersby and Openshaw, *J.*, 1949, 3207) does not bear materially on the interpretation of the search for amœbicides outlined above. [It is interesting to note that the central portion—within dotted lines in (III)—of the emetine structure contains the features of a partly decyclised ethylquinuclidine.]

All the above compounds with the exception of the diaminodecane contain secondary or tertiary nitrogen atoms. In the present work a study has been made of long-chain diamines containing two *primary* amino-groups and having the general formula $NH_2CHR{\cdot}[CH_2]_n{\cdot}CHR{\cdot}NH_2$. *In vitro* activities against *E. histolytica* found within the series are as high as 1 in 100,000.

As expected, simple polymethylene diamines of low molecular weight ($R = H$, $n = 1$ or 2) are inactive. With the introduction of alkyl groups having 4, 5, 6, or 8 carbon atoms, activity is consistently manifested when $n = 3$ (see Table). When $n = 4$ or 5 (see Table) the dystherapeutic effect of increasing molecular weight becomes evident and compounds 11 (R = 2-ethylhexyl; $n = 4$) and 14 (R = *n*-hexyl; $n = 5$) are inactive. This is an interesting result in view of the fact that the emetine molecule contains, apart from the methoxyl groups, a skeleton of 25 carbon atoms (compounds 11 and 14 have 22 and 19 carbon atoms, respectively). However, in emetine the two nitrogen atoms are separated by five carbon atoms, corresponding to $n = 3$ in our series.

The straight chain diamines are in several cases more active that the corresponding compounds with branched chains. Thus, the activities of compounds 1 (R = Bu^n; $n = 3$) and 3 (R = *n*-amyl; $n = 3$) are reduced when R becomes *iso*butyl and *iso*amyl, respectively (compounds 2 and 4).

The diamines were prepared (in the form of their hydrochlorides) by the following general procedure :

$$R{\cdot}CH(CO_2Et)_2 \longrightarrow (CO_2Et)_2CR{\cdot}[CH_2]_n{\cdot}CR(CO_2Et)_2 \longrightarrow CO_2H{\cdot}CHR{\cdot}[CH_2]_n{\cdot}CHR{\cdot}CO_2H \xrightarrow[\text{reaction}]{\text{Schmidt}} NH_2{\cdot}CHR{\cdot}[CH_2]_n{\cdot}CHR{\cdot}NH_2$$

All the compounds were tested as the water-soluble hydrochlorides.

In vitro *amœbicidal activities of dihydrochlorides of* $NH_2{\cdot}CHR{\cdot}[CH_2]_n{\cdot}CHR{\cdot}NH_2$.

Compound no.	*Diamines of the pentamethylene series* (n = 3).	R.	Activity.
1	5 : 9-Diaminotridecane	Bu^n	1 in 10,000
2	4 : 8-Diamino-2 : 10-dimethylundecane	Bu^i	1 in 1,000
3	6 : 10-Diaminopentadecane	*n*-amyl	1 in 100,000
4	5 : 9-Diamino-2 : 12-dimethyltridecane	*iso*amyl	1 in 10,000
5	7 : 11-Diaminoheptadecane	*n*-hexyl	1 in 100,000
6	7 : 11-Diamino-5 : 13-diethylheptadecane	2-ethylhexyl	1 in 100,000
	Diamines of the hexamethylene series (n = 4).		
7	5 : 10-Diaminotetradecane	Bu^n	1 in 10,000
8	6 : 11-Diaminohexadecane	*n*-amyl	1 in 10,000
9	5 : 10-Diamino-2 : 13-dimethyltetradecane	*iso*amyl	1 in 10,000
10	7 : 12-Diamino-octadecane	*n*-hexyl	1 in 100,000
11	7 : 12-Diamino-5 : 14-diethyloctadecane	2-ethylhexyl	inactive
	Diamines of the heptamethylene series (n = 5).		
12	5 : 11-Diaminopentadecane	Bu^n	1 in 10,000
13	4 : 10-Diamino-2 : 12-dimethyltridecane	Bu^i	1 in 10,000
14	7 : 13-Diaminononadecane	*n*-hexyl	inactive

Experimental.

Microanalyses by Drs. Weiler and Strauss.

Ethyl Alkanetetracarboxylates and Derived Acids.—Normal procedure was adopted for condensing polymethylene dibromides with the sodio-derivatives of substituted malonic esters (compare Perkin and Prentice, *J.*, 1891, **59**, 818). The following esters were thus prepared (yields are given in parentheses) and were hydrolysed to the tetracarboxylic acids by boiling them with alcoholic potassium hydroxide.

Ethyl tridecane-5 : 5 : 9 : 9-*tetracarboxylate* (25%), b. p. 198—202°/1 mm., 214—216°/4 mm., crystallised from methyl alcohol, melted at 35—37° (Found : C, 63·5; H, 8·6. $C_{29}H_{44}O_8$ requires C, 63·5; H, 9·3%). The derived *acid*, crystallised from water, had m. p. 149—151° (decomp.) (Found : C, 56·0; H, 7·8. $C_{17}H_{28}O_8$ requires C, 56·5; H, 7·8%).

Ethyl 2 : 10-*dimethylundecane*-4 : 4 : 8 : 8-*tetracarboxylate* (33%), crystallised from methyl alcohol, melted at 45—47°. Perkin and Prentice (*loc. cit.*) did not obtain a crystalline specimen. The derived *acid*, crystallised from aqueous acetic acid, had m. p. 148—150° (decomp.) (Found : C, 56·1; H, 7·8. $C_{17}H_{28}O_8$ requires C, 56·5; H, 7·8%). Perkin and Prentice (*loc. cit.*) prepared this acid but did not purify it or analyse it.

Ethyl pentadecane-6 : 6 : 10 : 10-*tetracarboxylate* (32·5%) had b. p. 234°/2 mm.; n_D^{15} 1·4492 (Found : C, 64·9; H, 9·2. $C_{31}H_{48}O_8$ requires C, 64·7; H, 9·6%). The derived *acid*, crystallised from dilute aqueous acetic acid, had m. p. 175·5° (decomp.) (Found : C, 58·4; H, 8·4. $C_{19}H_{32}O_8$ requires C, 58·7; H, 8·3%).

Ethyl 2 : 12-*dimethyltridecane*-5 : 5 : 9 : 9-*tetracarboxylate* (36%) had b. p. 225°/2 mm., n_D^{20} 1·4480 (Found : C, 65·0; H, 9·5. $C_{31}H_{48}O_8$ requires C, 64·7; H, 9·6%). The derived *acid*, crystallised from aqueous acetic acid, had m. p. 196—197° (decomp.) (Found : C, 57·3; H, 8·4. $C_{19}H_{32}O_8,\frac{1}{2}H_2O$ requires C, 57·4; H, 8·3%).

Ethyl heptadecane-7 : 7 : 11 : 11-*tetracarboxylate* (39%) had b. p. 254°/5 mm., 270°/9 mm., n_D^{17} 1·4530 (Found : C, 65·9; H, 9·9. $C_{33}H_{52}O_8$ requires C, 65·8; H, 9·9%). The derived *acid*, crystallised from dilute aqueous acetic acid, had m. p. 175—177° (decomp.) (Found : C, 60·6; H, 8·5. $C_{21}H_{36}O_8$ requires C, 60·5; H, 8·7%).

Ethyl 5 : 13-*diethylheptadecane*-7 : 7 : 11 : 11-*tetracarboxylate* (28·5%) had b. p. 258°/3 mm., n_D^{18} 1·4569 (Found : C, 68·2; H, 10·3. $C_{33}H_{56}O_8$ requires C, 67·8; H, 10·3%). The derived *acid*, crystallised from aqueous acetic acid, had m. p. 167—168° (decomp.) (Found : C, 63·7; H, 9·3. $C_{21}H_{40}O_8$ requires C, 63·5; H, 9·3%).

Ethyl tetradecane-5 : 5 : 10 : 10-*tetracarboxylate* (70%), crystallised from light petroleum (b. p. 40—60°), melted at 31—32° (Found : C, 64·0; H, 9·6. $C_{30}H_{46}O_8$ requires C, 64·1; H, 9·5%). The derived *acid*, crystallised from benzene–acetic acid, had m. p. 194—197° (decomp.) (Found : C, 58·0; H, 8·2. $C_{18}H_{30}O_8$ requires C, 57·7; H, 8·0%).

Ethyl hexadecane-6 : 6 : 11 : 11-*tetracarboxylate* (42%) had b. p. 244—246°/2 mm., n_D^{15} 1·4495 (Found : C, 65·8; H, 9·9. $C_{32}H_{50}O_8$ requires C, 65·5; H, 9·8%). The derived *acid*, crystallised from aqueous acetic acid, had m. p. 189—191° (decomp.) (Found : C, 60·0; H, 8·7. $C_{20}H_{34}O_8$ requires C, 59·7; H, 8·5%).

Ethyl 2 : 13-*dimethyltetradecane*-5 : 5 : 10 : 10-*tetracarboxylate* (46%) had b. p. 242°/3 mm., n_D^{15} 1·4465 (Found : C, 65·3; H, 9·7. $C_{32}H_{50}O_8$ requires C, 65·3; H, 9·8%). The derived *acid*, crystallised from

aqueous acetic acid, had m. p. 213° (decomp.) (Found : C, 59·3; H, 8·5. $C_{20}H_{42}O_8$ requires C, 59·7; H, 8·5%).

Ethyl octadecane-7 : 7 : 12 : 12-*tetracarboxylate* (45%) had b. p. 254—260°/5 mm., n_D^{15} 1·4510 (Found : C, 67·0; H, 10·3. $C_{36}H_{64}O_8$ requires C, 66·5; H, 10·0%). The derived *acid*, crystallised from aqueous acetic acid, had m. p. 194° (decomp.) (Found : C, 61·9; H, 8·7. $C_{28}H_{48}O_8$ requires C, 61·4; H, 8·8%).

Ethyl 5 : 14-*diethyloctadecane*-7 : 7 : 12 : 12-*tetracarboxylate* (50%) had b. p. 248°/1 mm., n_D^{24} 1·4562 (Found : C, 68·7; H, 10·5. $C_{44}H_{80}O_8$ requires C, 68·2; H, 10·4%). The derived *acid*, obtained as a glass which did not crystallise, gave a *silver* salt (Found : Ag, 46·9. $C_{36}H_{66}O_8Ag_2$ requires Ag, 47·2%).

Ethyl pentadecane-5 : 5 : 11 : 11-*tetracarboxylate* (70%), crystallised from light petroleum (b. p. 40—60°), melted at 44—46° (Found : C, 64·8; H, 9·5. $C_{31}H_{56}O_8$ requires C, 64·7; H, 9·6%). The derived *acid*, crystallised from aqueous acetic acid, had m. p. 169—171° (decomp.) (Found : C, 59·0; H, 8·3. $C_{19}H_{32}O_8$ requires C, 58·7; H, 8·3%).

Ethyl 2 : 12-*dimethyltridecane*-4 : 4 : 10 : 10-*tetracarboxylate* (70%), crystallised from light petroleum (b. p. 40—60°), melted at 63—65° (Found : C, 65·6; H, 9·2. $C_{31}H_{56}O_8$ requires C, 64·7; H, 9·6%). The derived *acid*, crystallised from benzene–acetic acid, had m. p. 153—155° (decomp.) (Found : C, 57·8; H, 8·4. $C_{19}H_{32}O_8,\frac{1}{2}H_2O$ requires C, 57·4; H, 8·3%).

Ethyl nonadecane-7 : 7 : 13 : 13-*tetracarboxylate* (50%) had b. p. 248—250°/2—3 mm., n_D^{15} 1·4550 (Found : C, 66·8; H, 9·7. $C_{39}H_{72}O_8$ requires C, 66·8; H, 10·1%). The derived *acid*, crystallised from benzene–acetic acid, had m. p. 174—176° (decomp.) (Found : C, 61·5; H, 8·8. $C_{31}H_{56}O_8$ requires C, 62·1; H, 9·1%).

Dicarboxylic Acids.—These were obtained in almost quantitative yield by heating the tetracarboxylic acids at a pre-determined optimum temperature which is given in parentheses immediately after the name of the acid

Tridecane-5 : 9-*dicarboxylic acid* (200°) crystallised from aqueous acetic acid in plates, m. p. 107—108° (Found : C, 66·7; H, 10·1. $C_{15}H_{28}O_4$ requires C, 66·1; H, 10·3%).

2 : 10-Dimethylundecane-4 : 8-dicarboxylic acid, crystallised from light petroleum (b. p. 80—100°), had m. p. 107—109° (Found : C, 66·7; H, 10·1. Calc. for $C_{15}H_{28}O_4$: C, 66·1; H, 10·3%) (Perkin and Prentice, *loc. cit.*, give m. p. indefinite, 82—84°).

Pentadecane-6 : 10-*dicarboxylic acid* (160°) crystallised from aqueous acetic acid in plates, m. p. 109—112·5° (Found : C, 67·9; H, 10·6. $C_{17}H_{32}O_4$ requires C, 67·9; H, 10·8%).

2 : 12-*Dimethyltridecane*-5 : 9-*dicarboxylic acid* (190°) crystallised from light petroleum (b. p. 60—80°) in shining plates, m. p. 140° (Found : C, 67·2; H, 10·6. $C_{17}H_{32}O_4$ requires C, 67·9; H, 10·8%).

Heptadecane-7 : 11-*dicarboxylic acid* (180°) crystallised from benzene in shining plates, m. p. 112—114° (Found : C, 70·0; H, 10·8. $C_{19}H_{36}O_4$ requires C, 69·4; H, 11·0%).

5 : 13-Diethylheptadecane-7 : 11-dicarboxylic acid (160°), obtained as an oil, gave a *silver* salt (Found : Ag, 36·1. $C_{23}H_{44}O_4Ag_2$ requires Ag, 36·0%).

Tetradecane-5 : 10-*dicarboxylic acid* (170°), crystallised from light petroleum (b. p. 40—60°), had m. p. 103—109° (Found : C, 66·9; H, 10·5. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·5%).

Hexadecane-6 : 11-*dicarboxylic acid* (190°), crystallised from light petroleum (b. p. 60—80°), had m. p. 99° (Found : C, 69·0; H, 10·7. $C_{18}H_{34}O_4$ requires C, 68·7; H, 10·9%).

2 : 13-*Dimethyltetradecane*-5 : 10-*dicarboxylic acid* (190°), crystallised from light petroleum (b. p. 60—80°), had m. p. 119—121° (Found : C, 69·0; H, 10·9. $C_{18}H_{34}O_4$ requires C, 68·7; H, 10·9%).

Octadecane-7 : 12-*dicarboxylic acid* (165°) crystallised from light petroleum (b. p. 40—60°) and had m. p. 97° in a sealed tube (Found : C, 70·0; H, 11·2. $C_{20}H_{38}O_4$ requires C, 70·1; H, 11·1%).

5 : 14-Diethyloctadecane-7 : 12-dicarboxylic acid (175°), obtained as an oil, gave a *silver* salt (Found : Ag, 35·0. $C_{28}H_{52}Ag_2$ requires Ag, 35·2%).

Pentadecane-5 : 11-*dicarboxylic acid* (160°) crystallised from aqueous acetic acid in rods, m. p. 90—94° (Found : C, 67·7; H, 10·8. $C_{17}H_{32}O_4$ requires C, 67·9; H, 10·8%).

2 : 12-*Dimethyltridecane*-4 : 10-*dicarboxylic acid* (160°), crystallised from aqueous acetic acid, had m. p. 111—112° (Found : C, 67·5; H, 10·4. $C_{17}H_{32}O_4$ requires C, 67·9; H, 10·8%).

Nonadecane-7 : 13-*dicarboxylic acid* (175°), crystallised from light petroleum (b. p. 40—60°), had m. p. 72·5—75·5° (Found : C, 69·1; H, 11·1. $C_{21}H_{40}O_4,\frac{1}{4}H_2O$ requires C, 69·0; H, 11·3%).

Diamines.—Schmidt's reaction was used for the preparation of the diamines from the long-chain dicarboxylic acids. Up to the present it had been applied only to three aliphatic dicarboxylic acids : succinic, adipic, and dodecane-1 : 12-dicarboxylic acid. The following general conditions were used : the dibasic acid was dissolved in concentrated sulphuric acid and benzene added (3—5 c.c. of acid and 3—6 c.c. of benzene for each g. of dibasic acid). Powdered activated sodium azide (Nelles, *Ber.*, 1932, **65**, 1345) was added (2—4 g.-mols. for 1 g.-mol. of dibasic acid) in small portions, with stirring at such a rate that the reaction mixture remained at a suitable temperature (usually *ca.* 30°). In a few cases the reaction mixture was subsequently warmed to a higher temperature to complete the reaction. Sodium hydroxide solution (30%) was added with strong cooling and the base extracted with benzene. Hydrogen chloride was passed into the dried extract and the precipitated hydrochloride separated.

5 : 9-Diaminotridecane was obtained as the hydrochloride (compound 1) from tridecane-5 : 9-dicarboxylic acid in 50—60% yield. The reaction was carried out at 35—45°. The *di*(*hydrogen oxalate*) crystallised from alcohol and had m. p. 198·5—199° (Found : C, 52·3; H, 8·2; N, 7·1. $C_{17}H_{34}O_8N_2$ requires C, 51·8; H, 8·7; N, 7·1%).

4 : 8-Diamino-2 : 10-dimethylundecane was obtained as the hydrochloride (compound 2) (decomp. above 225°) in 75% yield. The reaction mixture was heated to 45° to start the reaction but thereafter it proceeded smoothly at 30—32°. The *dipicrate* crystallised from aqueous ethyl alcohol in needles, m. p. 187—190° (Found : C, 44·9; H, 5·3; N, 16·5. $C_{28}H_{38}O_{14}N_8$ requires C, 44·6; H, 5·3; N, 16·6%).

6 : 10-Diaminopentadecane hydrochloride (compound 3) was obtained in 78% yield. The reaction was carried out at 25—30°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 130—133° (Found : C, 47·0; H, 5·4; N, 15·8. $C_{31}H_{44}O_{14}N_8$ requires C, 46·3; H, 5·7; N, 16·0%). The *diacetyl* derivative, crystallised from aqueous alcohol, had m. p. 179—180° (Found : N, 8·8. $C_{19}H_{38}O_2N_2$ requires N, 8·5%).

5 : 9-Diamino-2 : 12-dimethyltridecane hydrochloride (compound 4) was obtained in 80% yield. The reaction was carried out at 20—30°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 167—170° (Found : N, 15·9. $C_{31}H_{46}O_{14}N_8$ requires N, 16·0%).

7 : 11-Diaminoheptadecane hydrochloride (compound 5) was obtained in 75% yield, the reaction being carried out at 25—30°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 144—146° (Found : N, 15·2. $C_{39}H_{62}O_{14}N_8$ requires N, 15·3%). The *diacetyl* derivative, crystallised from aqueous ethyl alcohol, had m. p. 186° (Found : C, 70·9; H, 12·1; N, 7·7. $C_{31}H_{52}O_4N_2$ requires C, 71·1; H, 12·0; N, 7·9%).

7 : 11-Diamino-5 : 13-diethylheptadecane hydrochloride (compound 6) was obtained in 25—35% yield. The reaction was carried out at 25—30°. The *dihydrochloride* could only be isolated with water of crystallisation which it retained even after intensive drying *in vacuo*. It melted at 134—138° (Found : C, 60·4; H, 11·8; N, 6·8; Cl, 17·0. $C_{21}H_{44}N_2,2HCl,H_2O$ requires C, 60·4; H, 12·0; N, 6·7; Cl, 17·0%). The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 151—153° (Found : C, 50·3; H, 6·7; N, 13·8. $C_{39}H_{72}O_{14}N_8$ requires C, 50·5; H, 6·6; N, 14·2%).

5 : 10-Diaminotetradecane hydrochloride (compound 7) was obtained in 60% yield, the reaction being carried out at 25—30°. The *dipicrate*, crystallised from water, had m. p. 205—206° (Found : C, 45·8; H, 5·7; N, 16·5. $C_{26}H_{38}O_{14}N_8$ requires C, 45·4; H, 5·5; N, 16·3%).

6 : 11-Diaminohexadecane hydrochloride (compound 8) was obtained in 60% yield, the reaction being carried out at 25—30°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 155—158° (Found : C, 46·7; H, 5·7; N, 14·6. $C_{38}H_{60}O_{14}N_8$ requires C, 47·0; H, 5·9; N, 15·7%).

5 : 10-Diamino-2 : 13-dimethyltetradecane hydrochloride (compound 9) was obtained in 76% yield, the reaction being carried out at 25—30°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 205° (decomp.) (Found : C, 47·5; H, 5·8; N, 14·8. $C_{28}H_{42}O_{14}N_8$ requires C, 47·0; H, 5·9; N, 15·7%).

7 : 12-Diamino-octadecane (compound 10) was obtained as the picrate in 75—80% yield, the reaction being carried out at 25—30°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 176—180° (Found : C, 48·9; H, 6·1; N, 15·1. $C_{36}H_{56}O_{14}N_8$ requires C, 48·5; H, 6·2; N, 15·1%).

7 : 12-Diamino-5 : 14-diethyloctadecane hydrochloride (compound 11) was obtained in 70—87% yield, the reaction being carried out at 30—35°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 157—159° (Found : C, 51·1; H, 6·6; N, 14·0. $C_{34}H_{54}O_{14}N_8$ requires C, 51·1; H, 6·8; N, 14·0%). The *dihydrochloride* was prepared in benzene–carbon tetrachloride (Found : C, 64·1; H, 11·5; N, 6·6. $C_{22}H_{48}N_2,2HCl$ requires C, 63·9; H, 12·1; N, 6·7%).

5 : 11-Diaminopentadecane hydrochloride (compound 12) was obtained in 79% yield, the reaction being carried out at 25—30°. The *dipicrate*, crystallised from aqueous ethyl alcohol, had m. p. 198—199° (Found : C, 46·3; H, 5·9; N, 15·8. $C_{27}H_{42}O_{14}N_8$ requires C, 46·3; H, 5·7; N, 16·0%).

4 : 10-Diamino-2 : 12-dimethyltridecane hydrochloride (compound 13) was obtained in 50—55% yield, the reaction being carried out at 20—25°. The *dipicrate*, crystallised from water, had m. p. 194—195° (Found : C, 46·5; H, 5·7; N, 16·1. $C_{27}H_{42}O_{14}N_8$ requires C, 46·3; H, 5·7; N, 16·0%).

7 : 13-Diaminononadecane (compound 14) was obtained as the hydrochloride (m. p. 188—189°) in 80% yield, the reaction being carried out at 20—25°. The *dipicrate*, crystallised from benzene–ethyl alcohol, had m. p. 157—159° (Found : C, 49·6; H, 6·1; N, 14·4. $C_{31}H_{44}O_{14}N_8$ requires C, 49·2; H, 6·3; N, 14·8%).

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374. *Cation-exchange Resins. The Applicability of the Mass-action Law to the Exchange of Univalent Ions.*

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Methods are outlined for the determination of full exchange isotherms for univalent ions on ion-exchange resins.

The exchange of potassium, hydrogen, and ammonium ions on a sulphonated phenol–formaldehyde and a sulphonated cross-linked polystyrene resin has been studied. The nature of the resin and, in the case of the phenol–formaldehyde resin, its particle size have an effect on the affinity of the exchange process.

The applicability of the law of mass action to ion exchange is discussed and the findings of this investigation related to current theories of the mechanism of ion exchange.

ATTEMPTS have been made to predict and explain the behaviour of cation-exchange materials by using the Freundlich or Langmuir isotherms (Ungerer, *Kolloid. Z.*, 1925, **36**, 228; Boyd, Schubert, and Adamson, *J. Amer. Chem. Soc.*, 1947, **69**, 2818) or by assuming the operation of a Donnan equilibrium (Bauman and Eichhorn, *J. Amer. Chem. Soc.*, 1947, **69**, 2830). The phenomena of cation exchange can also be interpreted on a mass-action basis, and the mass-action law has been applied, with apparent success, to the more recent types of organic exchanger

materials (Boyd, Schubert, and Adamson, *J. Amer. Chem. Soc.*, 1947, **69**, 2818; Kressman and Kitchener, *J.*, 1949, 1190).

The mass-action treatment has advantages over others in simplicity and clarity and it enables a thermodynamic constant to be evaluated which should be characteristic of any exchange on a given exchanger. For example, for the exchange of univalent cations on the hydrogen form of a cation-exchange resin:

$$H_R + M^+_S \rightleftharpoons M_R + H^+_S$$

(subscript R denoting resin phase, S solution phase) we may write:

$$K_A = \frac{X_R}{1 - X_R} \cdot \frac{1 - X_S}{X_S} \cdot \frac{f_{M^+_S}}{f_{H^+_S}} \cdot \frac{f_{H_R}}{f_{M_R}}$$

(where X_S = molar fraction of the cation M^+ in solution; X_R = molar fraction of the cation M^+ on the resin; and $f_{M^+_S}$ and f_{M_R}, etc., are the appropriate activity coefficients of the ions in solution and on the resin).

(To calculate X_S and X_R, the total molarity of the solution with respect to M^+ and H^+ must be known and similarly the total molar capacity, C_R, of the resin for these ions.)

No satisfactory method for evaluating activities in the resin phase has yet been published and all that can be derived at present from experimental data is:

$$K' = \frac{X_R}{1 - X_R} \cdot \frac{1 - X_S}{X_S} \cdot \frac{f_{M^+_S}}{f_{H^+_S}} \quad \ldots\ldots\ldots\ldots \quad (1)$$

For the more common univalent ions in chloride solutions of total ionic strength less than 0·05 the ratio $f_{M^+_S}/f_{H^+_S}$ is only a few per cent. greater than unity and can generally be neglected without introducing serious error.

If an exchange isotherm for a resin is determined (the plot of X_R against X_S at a constant temperature) the value for K' can be calculated at any stage in the exchange process.

Kitchener and Kressman's work on the exchange of various cations with a sulphonated phenol–formaldehyde resin in its ammonium form indicated that the values of K' were practically constant, but the range of X_R values for which their constants were calculated was only about 0·4 to 0·7. Similarly, from the work of Boyd, Schubert, and Adamson the mass-action law would appear to be obeyed in the case of the sodium–hydrogen exchange over the range $X_R = 0{\cdot}3$ to $X_R = 0{\cdot}9$. However, in preliminary experiments in these laboratories on the exchange between hydrogen ions and the ions of lithium, sodium, potassium, ammonium, silver, and thallium on a sulphonated phenol–formaldehyde resin, it was found that values for K' varied considerably. In every case the value decreased by some 10—20% as X_R increased from 0·2 to 0·8.

A recent investigation by Duncan and Lister (*J.*, 1949, 3285; see also Faraday Society symposium on Chromatographic Analysis, 1949) on the exchange of sodium and hydrogen ions on Dowex 50 has confirmed the variability of the mass-action law constant with X_R, and Gregor (*J. Amer. Chem. Soc.*, 1948, **70**, 1293) predicts such a variability as a necessary outcome of most exchange processes.

The work described in this report was carried out with the object of determining the extent of the variability of K', as it is of considerable practical importance to know precisely what significance can be attributed to a mass-action law constant. This investigation has been restricted to an examination of the exchange of potassium, hydrogen, and ammonium ions (especially the first two) on two types of resin, a sulphonated cross-linked polystyrene and a sulphonated phenol–formaldehyde resin. The results reported here largely confirm the findings of Duncan and Lister and in addition may throw some light on apparent anomalies in the results of various workers in this field.

General Technique.

A. *Progressive-batch Method.*—A sample of 2—5 g. of dry hydrogen-form resin, of exchange capacity C_R milliequivalents (an amount possessing an exchange capacity of about 10 milliequivalents should be used), is placed in a dry 250-ml. conical flask, and V ml. of a solution of the exchanging ion M^+, diluted to 125 ml. with water, are added. The solution of M^+ used contains m milliequivalents of ion per ml. The resin and solution are then shaken mechanically in a thermostatically controlled water-bath until no further exchange takes place.

A fraction, f, of the resulting solution is removed and the number of milliequivalents of

hydrogen ion, x_1, in this aliquot determined by titration with standard alkali (approximately 0·05N.). If the resin is in the form of fine particles the aliquot, f, should be pipetted through a small sinter kept permanently in the flask.

To the remaining solution in contact with the resin b . Y ml. of standard M^+ solution are added and the volume again adjusted to 125 ml. with water. After equilibrium has been reached for the second time at the correct temperature a further aliquot f is removed and the number of milliequivalents of hydrogen ion now present, x_2, determined.

Similarly for the nth experiment, b^{n-1} . Y ml. of M^+ solution are added and the number of milliequivalents of H^+, x_n, in the nth aliquot is determined by titration. With such an experiment it can be proved that after the nth exchange

$$X_{\mathbf{R}_n} = \left(f \cdot \sum_{i=1}^{i=n-1} (x_i) + x_n\right) \Big/ f \cdot C_{\mathbf{R}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and

$$X_{\mathbf{S}_n} = 1 - \{x_n(1 - f - b)/f.m.Y[(1 - f)^n - b^n]\}$$

The expression for $X_{\mathbf{S}_n}$ can be simplified by grouping the constants to form a factor t_n, where $t_n = (1 - f - b)/f[(1 - f)^n - b^n]$, which can be calculated for each value of n when the values for f and b are decided upon, and hence:

$$X_{\mathbf{S}_n} = 1 - t_n \cdot x_n/m \cdot Y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Thus by use of equations 2 and 3 an isotherm can easily be constructed from a series of simple titration experiments. For most univalent exchanges it is found that a value of 1·25 for b gives a suitable spacing of points on an isotherm. In order to keep the total ionic strength of solutions to a minimum, so as to avoid the necessity of making activity corrections, f should be at least 0·8 (a 100 ml. portion from 125 ml. has been used in this work). The best value for Y depends upon the value for K' and it can be shown that for the first point on the isotherm to be at $X_{\mathbf{R}} = 0{\cdot}125$, Y should be equal to $(C_{\mathbf{R}}/56K' \cdot m)(1 + 7K')$. Clearly b^{n-1} . Y must not exceed 100 ml., *i.e.* Y should not be greater than about 15 ml. for an 8-point isotherm.

A technique similar to that outlined above can be used when the resin is in the M^+-saturated form, b^{n-1} . Y ml. of acid solution containing m milliequivalents of H^+ per ml. being added, and the number of the milliequivalents of hydrogen ions in the aliquot f again being determined. These experiments check the "forward" isotherm (first point $X_{\mathbf{R}} = 0{\cdot}125$) by a "back" isotherm (first point $X_{\mathbf{R}} = 0{\cdot}875$). The formulæ for calculating $X_{\mathbf{R}_n}$ and $X_{\mathbf{S}_n}$ are similar to 2 and 3 above, viz:

$$X_{\mathbf{R}_n} = \left(\sum_{i=1}^{i=n} (m \cdot Y)b^{i-1} - \sum_{i=1}^{i=n-1} (x_i) - x_n/f\right) \Big/ C_{\mathbf{R}} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$X_{\mathbf{S}_n} = 1 - t_n \cdot x_n/m \cdot Y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

with the m and Y values referring to the acid added.

The value for $C_{\mathbf{R}}$ used in equations (2) and (4) is best determined from the titrations actually made during the determination of the isotherm. For example, if after the determinations of the last point on a "forward" isotherm of the exchange of M^+ with $H_{\mathbf{R}}$, the resin is transferred quantitatively to a tube and the remaining hydrogen ion eluted by a strong solution of M^+, then:

$$C_{\mathbf{R}} = \sum_{i=1}^{i=n-1} (x_i) + \frac{x_n}{f} + E$$

where E is the number of milliequivalents of hydrogen ions removed from the resin.

Clearly, although most convenient for exchanges involving the hydrogen ion, the technique outlined above can be used for any other univalent exchange, the titration with standard alkali being replaced by a suitable determination of the ion used in place of the hydrogen ion.

It has been found that, owing to experimental errors, accurate values of K' cannot be calculated from the first point in either the "forward" or "backward" determination and, for the same reason, no value for $X_{\mathbf{S}}$ outside the range 0·125—0·90 should be used. All points on the isotherm of $X_{\mathbf{R}}$ value greater than 0·9 or less than 0·2 should be rejected.

B. *Single-batch Method.*—To check any one point on an isotherm, the $X_{\mathbf{R}}$ and the $X_{\mathbf{S}}$ value can be determined in a single experiment by equilibrating a resin of known capacity, $C_{\mathbf{R}}$ milliequivalents, with a solution of known initial $X_{\mathbf{S}}$ value and determining the amount of one of the ions remaining in the solution. Thus if a solution which initially contains A milliequivalents

of M^+ and B_1 milliequivalents of H^+ is equilibrated with a resin in the hydrogen form and is thereafter found to contain B_2 milliequivalents of H^+

$$X_2 = (A + B_1 - B_2)/(A + B_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$X_2 = (B_2 - B_1)/C_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

If the amount of M^+ in the solution in equilibrium with the resin is also directly determined and not assumed to be equal to $A - (B_2 - B_1)$, then a complete check can be made on the quantitative nature of the exchange and any adsorption phenomena revealed. As deposition on apparatus walls, etc., can be assumed to be absent with univalent ions, it is not necessary to analyse directly the resin phase. Such analysis would probably only introduce unnecessary error.

Although useful for single-value determinations and for the confirmation of quantitative ion exchange, the above technique is less suitable than the progressive-batch method when it is desired to determine a complete isotherm. The progressive batch method is considerably more rapid and convenient, and is more economic in the use of both resin and exchanging ions.

C. *Column Method.*—The progressive-batch method is not sufficiently accurate for a satisfactory determination of points at either extreme of an isotherm, *i.e.*, where X_2 is less than 0·2 or greater than 0·9, and the single-batch method necessitates the use of undesirably concentrated solutions and is somewhat inconvenient when several determinations have to be made. For the determination of X_2 and X_2 at either end of the isotherm a procedure has been devised in which a solution of known X_2 value is used and the X_2 value of the resin in equilibrium with this solution is determined.

In this method, which will be called the column method, about 10 milliequivalents of resin are placed in a glass tube so as to make a column 5—10 cm. long. The column is jacketed with water at a thermostatically controlled temperature and a solution of known X_2 composition and correct temperature is poured through the tube at a rate of 5—6 ml. a minute until the resin has assumed the correct equilibrium composition. The resin used is initially saturated by the ion of which it will finally contain most. Finally the resin is slowly washed with water until the eluent is ion-free.

To ensure reasonably rapid attainment of equilibrium at least 0·2M-solutions must be used. These are too strong for activity corrections to be neglected but the resin while being washed will to some extent equilibrate with progressively more dilute solutions until its composition is probably not far removed from the " ideal " value.

Points on an isotherm can now be plotted, as the values for X_2 are already known and the X_2 values can be obtained by suitable analysis of the resin column. For example, if the column has been used to obtain an X_2 value for the H_2 to M_2 change with X_2 small, the M on the resin is eluted by strong acid and the eluent analysed for this ion. The total capacity of the resin in the column is then determined by eluting it with a strong solution of M^+ ions and determining the amount of acid in the eluent. The resin is then in a condition in which it can be used to obtain a point at the other end of the isotherm.

Experimental.

Materials Used.—Potassium and ammonium ions were used as standard solutions prepared directly from the dried AnalaR quality chlorides. Hydrochloric acid solutions were prepared from AnalaR material and standardised against anhydrous sodium carbonate.

The resins used were Zeo-Karb 215, a sulphonated phenol–formaldehyde manufactured by Permutit Ltd., and a sulphonated cross-linked polystyrene of a similar type to Dowex 50. The latter, which was prepared at the Chemical Research Laboratories, Teddington, and supplied by courtesy of the Director, will be referred to as the C.R.L. resin. It was used, as received, in the form of spherules of uniform size (passing B.S. 100 sieve but retained by B.S. 150) the capacity being about 5 milliequivalents per g. of dry resin. The Zeo-Karb resin was carefully ground and two fractions used, one passing B.S. sieve 12 but retained in B.S. 25 and the other passing B.S. 60 but retained on B.S. 150. These fractions will be referred to as coarse and fine Zeo-Karb, respectively. The capacity of the Zeo-Karb resin was about 2 milliequivalents per g. of dry resin. Before use the resins were packed into columns and eluted alternately with 2N-sodium chloride solution and 2N-hydrochloric acid, the cycle being repeated at least twice. The resins were finally washed thoroughly with re-distilled water.

Conditions for Equilibrium.—In the single- and progressive-batch experiments it was found that no appreciable increase in the amount of exchange took place after shaking the resins for 1½ hours in contact with a solution of potassium chloride.

This was shown to apply to both the coarse Zeo-Karb and the C.R.L. resin at 20°, and to apply irrespective of whether the resin was in the hydrogen or potassium form. All batch experiments were therefore assumed complete after 100 minutes' shaking.

In the column experiments the composition of the resin was the same whether 1000 ml. or 500 ml. of solution had passed, and the latter volume was therefore assumed to be sufficient.

FIG. 1.

K^+/H^+ *exchange on fine Zeo-Karb* 215 *at* 20°.

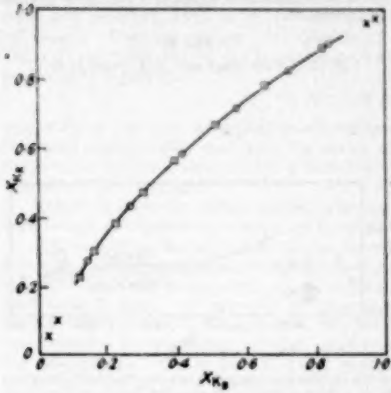


FIG. 2.

K^+/H^+ *exchange on coarse Zeo-Karb* 215 *at* 20° *and* 30°.

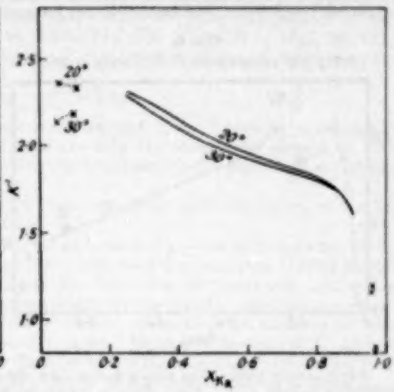


FIG. 1. ○ *Forward progressive batch.* ⊡ *Backward progressive batch.* × *Column.*

FIG. 3.

K^+/H^+ *exchange on fine Zeo-Karb* 215 *at* 20° *and* 30°.

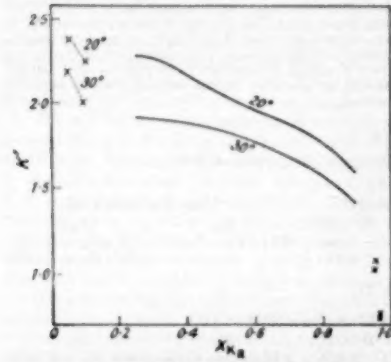
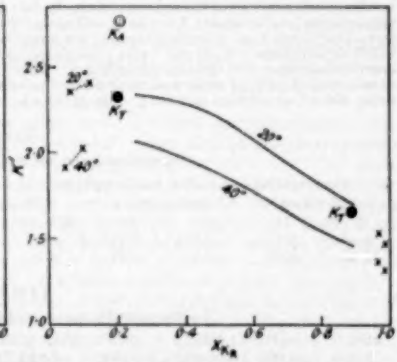


FIG. 4.

K^+/H^+ *exchange on C.R.L. resin at* 20° *and* 40°.



A slight hydrolytic decomposition of the Zeo-Karb resin when in the hydrogen form was initially rather confusing and mistaken for continued exchange. However, it was found that this hydrolysis could be corrected for in progressive-batch experiments by carrying out a blank. The amount of acid in this blank was proportional to the fraction of resin in the hydrogen form and hence suitable corrections could be made at any X_R value from a blank carried out on the resin entirely in the hydrogen form.

Methods of Analysis.—Hydrogen-ion concentrations were determined in all experiments by titration with standard alkali.

The ammonium-ion concentration was determined volumetrically by the addition of a known excess of standard alkali followed by determination of the amount left after removal of ammonia by boiling. When hydrochloric acid was also present any large excess of this acid was removed by careful evaporation, and the remainder neutralised before addition of the standard alkali.

Potassium, when present only with hydrochloric acid, was determined by removing all acid by repeated evaporation with water, and then estimating the chloride left by titration with mercuric nitrate.

A blank compensated for traces of non-volatile chlorides formed by the action of hydrochloric acid on glass, etc. When potassium was present with ammonium salts the latter were replaced by sodium by boiling the solution with sodium hydroxide solution and the potassium in the resulting mixture determined as the perchlorate. After the salts had been heated to fuming with a very slight excess of perchloric acid to convert the chlorides into perchlorates, these were extracted with dry ethyl acetate to remove the sodium salt. To compensate for traces of potassium and ammonium introduced during the analysis, each determination was standardised by the simultaneous analysis of a synthetic mixture of similar composition, containing a known amount of potassium.

FIG. 5.

NH_4^+/H^+ *exchange on C.R.L. resin at 20°.*

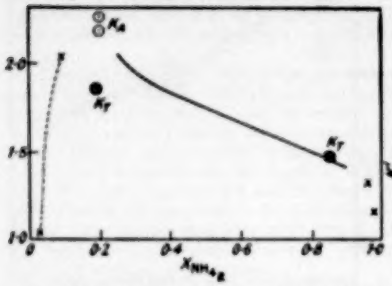
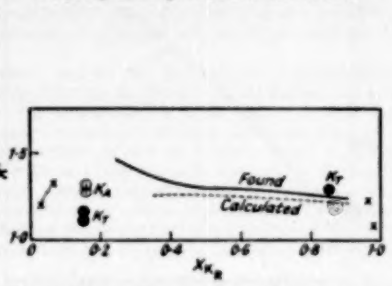


FIG. 6.

K^+/NH_4^+ *exchange on C.R.L. resin at 20°.*



Experimental Data.—The experimental data obtained in this investigation are summarised diagrammatically in Figs. 1—6. Fig. 1 shows a typical isotherm obtained by the progressive-batch method with points obtained by column experiments at each end. Mass-law constants for each exchange studied have been calculated at regular X_R intervals from the best curve through the plot of progressive-batch experimental data. A plot of K' against X_R is shown by the continuous lines in Fig. 2—6. K' values from column experiments are shown in these diagrams by crosses.

In addition to the above experiments; single-batch experiments were made with all the exchanges possible between potassium, hydrogen, and ammonium ions, by using the C.R.L. resin at 20°. The results of full analyses of the aqueous phases, before and after exchange, are shown in Tables I—III. Two mass-action law constants have been calculated from these data. K_A is the value which would be calculated solely from a consideration of the quantities of exchanged ion,* as is done in the progressive-batch experiments. K_F is the " true " exchange constant calculated from a consideration of the actual ionic composition of both resin and solution. These two K values are also shown in Figs. 4—6. 250 Ml. of solution and 3 g. of resin were used in the experiments at low X_R; in the experiments at high X_R value 400 ml. of solution and 1·5 g. of resin were employed.

TABLE I.

Potassium hydrogen exchange, C.R.L. resin at 20°.

Composition of solution (milliequivalents of ion), initial solution.		final solution.		Exchange.		Mass-law constants,	
K^+.	H^+.	K^+.	H^+.	K^+ (on).	H^+ (off).	K_A.	K_F.
3·004	5·120	0·808	7·410	2·196	2·290	2·77 (X_R = 0·211)	2·32 (X_R = 0·202)
25·00	0·00	20·69	4·34	4·31	4·34	—	1·66 (X_R = 0·888)

TABLE II.

Ammonium/hydrogen exchange, C.R.L. resin at 20°.

NH_4^+.	H^+.	NH_4^+.	H^+.	NH_4^+ (on).	H^+ (off).	K_A.	K_F.
3·000	5·000	0·917	7·175	2·083	2·175	2·18 (X_R = 0·200)	1·86 (X_R = 0·192)
3·004	5·120	0·932	7·310	2·072	2·190	2·26 (X_R = 0·201)	1·85 (X_R = 0·191)
24·98	0·00	19·95	5·04	5·03	5·04	—	1·47 (X_R = 0·853)

TABLE III.

Potassium/ammonium exchange, C.R.L. resin at 20°.

K^+.	NH_4^+.	K^+.	NH_4^+.	K^+ (on).	NH_4^+ (off).	K_A.	K_F.
3·000	7·000	1·347	8·740	1·653	1·740	1·32 (X_R = 0·160)	1·17 (X_R = 0·153)
3·000	7·000	1·390	8·70	1·610	1·700	1·28 (X_R = 0·160)	1·12 (X_R = 0·152)
25·00	0·00	20·35	4·56	4·65	4·56	—	1·30 (X_R = 0·852)

* When an ion M_1^+ displaces an ion M_2^+ from a resin the reaction will be referred to for brevity as the M_1^+/M_2^+ exchange, M_1^+ being called the exchanging ion and M_2^+ the exchanged ion.

Discussion.

It is clear from the figures that no mass-action law constant for the simple exchanges studied in this investigation can be calculated by using equation (1). Although, as suggested by Kitchener and Kressman (*loc. cit.*), changes of activity of an ion in solution may be compensated for by activity changes of the ion in the resin phase, the activity of the resin phase *per se* is itself not constant, even in dilute solutions, and varies with the ionic composition of the exchanger. This has already been considered by Kieland (*J. Soc. Chem. Ind.*, 1935, **54**, 232; *Tids. Kjemi*, 1935, **15**, 74) for inorganic exchangers. The correction suggested by him, which leads to the expression:

$$\log K' = \log Ka - C(1 - 2X_B)$$

where Ka is the true thermodynamic exchange constant and C an "activity correction" constant, applies fairly well over the range $X_B = 0{\cdot}35$—$0{\cdot}75$ but fails badly outside it. At present it is doubtful whether any practical activity correction can be devised which will apply over the whole isotherm.

In part at least this is due to phenomena other than true exchange taking place, as will be seen from a consideration of the experimental data.

The K' values obtained from column experiments at a small X_B value were determined by measuring the amount of exchanging ion on the resin, and they thus measure true exchange together with any adsorption of the exchanging ion. In these circumstances adsorption equivalent to only a few per cent. of the exchange capacity of the resin is sufficient to cause a considerable increase in the apparent value of K'. A similar measurement is made in Duncan and Lister's "break-through volume" method and from the "hump" in the plot of K' against X_B obtained by these authors it would appear that, in the sodium/hydrogen exchange, true exchange is taking place together with a variable amount of adsorption, the latter being at a maximum at $X_B = 0{\cdot}1$—$0{\cdot}2$. In our own investigation points to the left of such a maximum have in general been obtained, although for the exchange on coarse Zeo-Karb at 20° and fine Zeo-Karb at 20° and 30° the points appear to be situated on the peak or to the right thereof. Apart from adsorption phenomena it may well be that the true exchange constant is itself decreasing with X_B, as witness the exceptionally low value of K' at $X_B = 0{\cdot}024$ in the NH_4^+/H^+ exchange (Fig. 5).

K' values from progressive-batch experiments, over the range $X_B = 0{\cdot}4$—$0{\cdot}9$, approximate closely to true exchange constants. This is probably also the case with K' values obtained from column experiments at high X_B. The latter have been calculated from a determination of the quantity of exchanged ion still left on the resin and could therefore be spuriously low in the event of an adsorption of the exchange ion taking place.

The K_T values from single-batch experiments also confirm, within experimental error, the general trend of the isotherms, but it will be noted that the K' values are high and there appears to be more exchanged ion leaving the resin than exchanging ion going on to it. This effect is probably the result of water being absorbed by the resin and not, as might be supposed, from a desorption of exchanged ion. In those experiments shown in the tables which were made at a low X_B value 3 g. of air-dried resin were added to 250 ml. of solution. The amount of pure water absorbed from the electrolyte solution by this resin is difficult to estimate exactly but it is probably sufficient (1·5—2·5 ml.) to account for the apparent non-equivalence of exchange and to reduce K_A values to those of K_T, the latter being substantially unchanged.

Methods depending solely upon the measurement of the exchanged ion in an aliquot of solution are therefore very sensitive at low X_B to the absorption of water by the resin, unless a very high liquid-to-resin ratio is maintained or the amount of pure water effectively withdrawn into the resin phase is accurately known. With the column experiments this error is not incurred and by neglecting it in the progressive-batch experiments the general shape of the K' against X_B plot is not significantly changed except at low X_B values. The first plotted points are here probably sufficiently in error to account for the comparatively sudden rise in K' found in some experiments at values of X_B less than $0{\cdot}3$—$0{\cdot}4$. Values from K' at $X_B = 0{\cdot}5$ would be only 2—3 per cent. too large.

Apart from the above outline of exchange behaviour, some of which requires further experimental confirmation, there are certain other points of interest arising from this work.

The whole question of the mechanism of ion exchange has recently been dealt with by two different methods of approach. Kitchener and Kressman have suggested that a univalent-ion exchange may arise chiefly from the difference in coulombic energy of the two possible ion-resin electrostatic bonds. Presumably this energy difference is responsible for much of

the maximum work of the exchange, any expansion or contraction of the resin matrix being ignored. On the other hand Gregor (*J. Amer. Chem. Soc.*, **1948**, **70**, **1293**) interprets exchange phenomena on the basis of osmosis, no direct interaction of exchanging and fixed " resin ions " being postulated. The resin is said to undergo a volume change ($V_{M^+_1} - V_{M^+_2}$) due to osmotic pressure, and by equating the virtual osmotic and PV work at equilibrium the expression :

$$RT \ln (a_{M^+_1}/a_{M^+_2})_R \cdot (a_{M^+_2}/a_{M^+_1})_S = p(V_{M^+_1} - V_{M^+_2})$$

is derived, where p is the swelling pressure.

It is of interest that both the above interpretations can be considered to be based upon the relationship :

$$\Delta G = \Delta A + \int p \mathrm{d}v.$$

where $\int p\mathrm{d}v$ is the work done against the external osmotic pressure, p, ΔG is the free energy and ΔA the work function. According to the first interpretation, ΔG is assumed to be equivalent to the maximum work done in replacing one ionic binding with another, assuming no significant volume changes; according to the second, the maximum work function term is neglected and the change in free energy assumed equal to the work of contraction or expansion of the resin against osmotic pressure. The two mechanisms are not necessarily mutually exclusive and it would be desirable to know to what extent they each contribute to exchange phenomena. The data for evaluating the difference in coulombic energy of ions as they exist on the resin are not known and it remains to be seen precisely how well affinity constants can be predicted from osmotic data.

The results of the present work are of some value in deciding which of the two mechanisms predominates during exchange from dilute aqueous solutions.

In the absence of activity correction data, true thermodynamic constants cannot be evaluated from K', but for comparison purposes between different resins etc., by using the same exchange reaction, it is probably legitimate to make use of the exchange constants at some fixed X_R value, say 0·5. Thus with the potassium/hydrogen exchange on the C.R.L. resin and on the coarse and fine Zeo-Karb 215 resin (Fig. 2, 3, and 4) it will be seen that data are available for calculation of the standard decrease of free energy of exchange, $-\Delta G^\circ$. If the simple form of the reaction isochore can be used over the temperature range 20—40° an approximate value for the heat of reaction ΔH° may also be computed and hence the change of " bound heat " $T\Delta S^\circ$ evaluated from the equation $-\Delta G = -\Delta H + T\Delta S$. The approximate values of $-\Delta G^\circ$, $-\Delta H^\circ$, and $-T\Delta S^\circ$ at 20° for X_R 0·5 are given in Table IV.

TABLE IV.

Resin.	$-\Delta G^\circ$ (kcals.).	$-\Delta H^\circ$ (kcals.).	$-T\Delta S^\circ$ (kcals.).
C.R.L.	0·46	1·45	1·0
Fine Zeo-Karb 215	0·42	2·0	1·6
Coarse Zeo-Karb 215	0·41	0·25	−0·15

It will be seen that the decrease of free energy at 20° is significantly greater with the polystyrene resin than with Zeo-Karb 215, and this has been found to be the case with all univalent-ion exchanges studied. One explanation of such behaviour is that there is an appreciable difference in the " distance of least separation " of the two exchanging ions (or the sulphonic groups on the resin) in the two materials. Alternatively, the difference could be explained by the increase in expansion possible with the more elastic polystyrene resin and it would be interesting to determine the variation of exchange constant with the degree of cross linkage of these polymers.

The most striking feature shown in Table IV, however, is the significant differences in the decrease of bound heat in the three reactions studied. This not only varies from the one resin to the other but, more important, is markedly different with the two samples of Zeo-Karb 215. These were from the same bottle of resin and differed only in particle volume (by a factor of about 50—100). As mentioned by Kitchener and Kressman, if entropy changes in the resin can be ignored this alteration of bound heat must arise from a change in the degree of hydration of the ions during the exchange. A change of only 1—2 kcals., however, seems rather small considering that the heat of hydration of these ions is of the order of 100—200 kcals. and even if the differences in hydration varied for the same exchange on two essentially different types of resin, it is difficult to understand how a relatively small particle-size variation in the same

sample of resin could have any effect. On the other hand, if part at least of the entropy change were associated with resin expansion and contraction, the variation between the two types of resin and between the two samples of the same resin would be more easily understandable. In the latter case, although ideally the change of bound heat for a gram-equivalent exchange should not depend upon the subdivision of the exchanger, in practice the differences of internal strain and surface energy, etc., between bulks of resin comprised of large and small pieces might well give rise to such an effect.

There remains to be considered the marked variation of K' with X_B. This may arise from a progressive decrease in the effective radius of the hydrogen ion in comparison with that of the potassium ion, but, as mentioned above, one would expect significant changes of this nature to be accompanied by a considerable heat of reaction. Gregor explains the variation on the grounds that the virtual pV work is not a constant and varies with the degree of exchange. Certainly the very marked difference between the behaviour of the C.R.L. and the Zeo-Karb resins at high X_B might well arise from the difference in elastic properties of these materials.

Whichever mechanism predominates the potassium/ammonium exchange (between ions of similar radii whether hydrated or otherwise) would be expected to be nearly unity and to vary little with X_B. It is interesting to note that the variations of K' with X_B for the potassium/hydrogen and ammonium/hydrogen exchanges, over the portion of the isotherm unaffected by any water absorption, effectively compensate each other. Values for K' for the potassium/ammonium exchange calculated from the ratio of these constants, as if they were true thermodynamic constants at any X_B value, are in excellent agreement with the experimentally determined figures (see Fig. 6).

Thus, although they are not, strictly speaking, thermodynamic constants, the values for K' at an X_B value of about 0·5 are of practical use in comparing exchange behaviour between various pairs of ions and various exchangers. However, the use of constants determined in this region for the prediction of analytical separations by, for example, Mayer and Tompkins's method (*J. Amer. Chem. Soc.*, **1947**, **69**, 2866) is impracticable. Affinity constants for use when working at either end of the isotherms must be determined under conditions approximating as nearly as possible to those to be used during the proposed separation.

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Chemical Inspectorate, Royal Arsenal, Woolwich. [*Received, January 5th*, 1950.]

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375. *Synthesis of Some Glyoxalino*(1′ : 2′-1 : 2)*quinolines.*

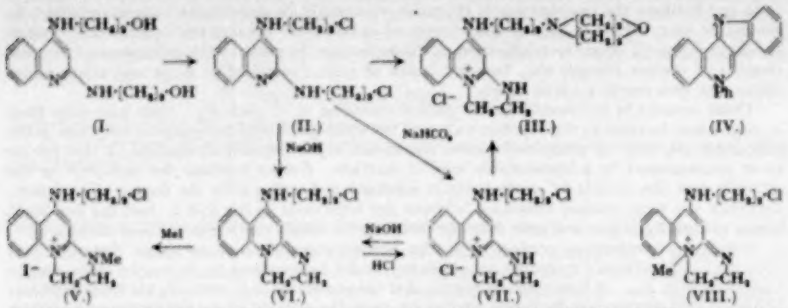
By J. M. Osbond.

In an attempt to prepare quinoline derivatives with two basic side chains, 2 : 4-dichloroquinoline was readily converted into the corresponding 2 : 4-di-(2-chloroethylamino)quinoline hydrochloride. The base (II) derived from this, however, under the influence of bases such as morpholine or aqueous alkalis yielded a dihydroglyoxalinoquinoline by cyclisation of the side chain in the 2-position with the quinoline-nitrogen atom. Some reactions and derivatives of this type of ring system are described.

It has been demonstrated (Fulton, Joyner, King, Osbond, and Wright, *Proc. Roy. Soc.*, **1950**, *B*, in the press) that certain 4-alkylaminoethylaminoquinaldines display high action against *Entamœba histolytica in vitro*, approaching in some cases the activity of emetine. In an attempt to extend this work, it was thought to be of interest to prepare 2 : 4-di(alkylaminoethylamino)-quinolines. It was hoped that 2 : 4-di-(2-chloroethylamino)quinoline hydrochloride (cf. II) would, when condensed with various primary and secondary amines, afford a series of homologous quinolines. 2 : 4-Di-(2-hydroxyethylamino)quinoline (I), which was readily prepared by heating 2 : 4-dichloroquinoline with an excess of ethanolamine, was identical with a specimen previously obtained as a by-product in the condensation of ethanolamine and 2-anilino-4-chloroquinoline (Fulton *et al.*, *loc. cit.*).

This dihydroxy-base (I) with phosphorus oxychloride gave the hydrochloride of the corresponding dichloro-compound (II) in good yield. When this hydrochloride was condensed with morpholine the expected dimorpholino-derivative was not obtained. Instead, a quaternary chloride was isolated as the hydrochloride, $C_{17}H_{22}ON_4Cl.HCl$: the chlorine atom of the side-chain in the 4-position had been replaced by the morpholino-radical whereas the chlorine atom

in the side chain in the 2-position had formed a quaternary salt with the ring nitrogen atom, thus giving 4′ : 5′-dihydro-4-(2-morpholinoethylamino)glyoxalino(3′ : 2′-1 : 2)quinolinium

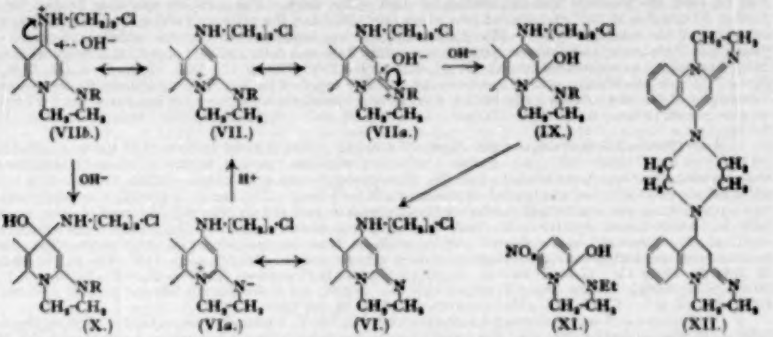


chloride hydrochloride (cf. III). When a solution of the hydrochloride of (II) was treated with cold saturated sodium hydrogen carbonate solution, the base (II) separated as a pale yellow oil which, if left in contact with the aqueous solution, soon dissolved. The oil could however be isolated by rapid extraction with ether, but the solution thus obtained, when kept at room temperature, soon became cloudy and deposited 4-(2-chloroethylamino)-4′ : 5′-dihydroglyoxalino(3′ : 2′-1 : 2)quinolinium chloride (VII) as colourless crystals, readily soluble in water, in which they gave rise to chlorine ions. When, however, dilute aqueous sodium hydroxide solution was added to a solution of the hydrochloride of (II) a colourless oil separated which rapidly became yellow; on gentle warming of the mixture for a short while, the oil solidified to a yellow solid melting above 320°. This contained halogen but not in an ionic form, and is the anhydronium base, 4-(2-chloroethylamino)-4′ : 5′-dihydroglyoxalino(1′ : 2′-1 : 2)quinoline (VI); with dilute hydrochloric acid, it gave (VII). Similarly, although the quaternary chloride (VII) was stable to sodium hydrogen carbonate solution, addition of aqueous sodium hydroxide gave (VI) which was identified by reconversion into (VII) and was further characterised as the corresponding quaternary bromide (cf. Armit and Robinson, *J.*, 1925, 1604; Holt and Petrow, *J.*, 1948, 922). Treatment of the quaternary salt (VII) with hot dilute alkali for a longer period gave an amorphous material insoluble in all the normal solvents and no longer giving a crystalline hydrochloride.

Since (VII) is readily converted into (VI), formation of the anhydronium base (VI) by treatment of the salt (II) with sodium hydroxide probably proceeds by way of (VII). The interconversion of (VI) and (VII) probably proceeds by the mechanism formulated below. The quaternary salt has the resonance forms (VII, VII*a*, and VII*b*; R = H), resembling those of an amidine salt, and gives in the presence of hydroxyl ions a quaternary hydroxide which readily loses water in its pseudo-base form (IX; R = H) to give the anhydronium base. This base can also exist in three resonance forms, two of which are (VI) and (VI*a*), and by the addition of a proton gives the quaternary salt (VII). Since the pseudo-base (IX; R = H) is a possible intermediate in the conversion of (VII) into (VI) an attempt was made to isolate it by treating (VII), in the cold, with alkali and then immediately extracting the base with chloroform. However, only the anhydronium base was isolated. Since, moreover, pseudo-bases readily form the corresponding methoxy- or ethoxy-derivative in the presence of methyl or ethyl alcohol respectively (cf. Decker, *Ber.*, 1900, **33**, 1715; *J. pr. Chem.*, 1892, **45**, 182; Holt and Petrow, *J.*, 1948, 919), a solution of the quaternary chloride (VII) in ethyl alcohol was made just alkaline with dilute aqueous sodium hydroxide and set aside at room temperature. From this a yellow crystalline material was isolated which did not contain halogen and in water gave a strongly alkaline solution. Analysis indicated it to be 1 : 4-bis-[4′ : 5′-dihydroglyoxalino(1′ : 2′-1 : 2)quinol-4-yl]piperazine (XII) derived from two molecules of (VI) by loss of hydrogen chloride (cf. Knorr, *Ber.*, 1905, **38**, 3135; 1906, **39**, 1420; Hanby and Rydon, *J.*, 1947, 513).

With methyl iodide at room temperature (VI) gives a quaternary methiodide, which is formulated as 4-(2-chloroethylamino)-4′ : 5′-dihydro-1′-methylglyoxalino(3′ : 2′-1 : 2)quinolinium iodide (V), rather than the alternative (VIII). It has already been shown that the yellow anhydronium base (VI) gives by proton addition, colourless salts (VII) thus allowing the quinoline system to re-establish its conjugated structure; it therefore seems probable that

addition of methyl iodide (VI) will similarly give the more stable structure (V) rather than retain the less stable arrangement of bonds represented by (VIII). It is interesting that Mann (*J.*,



1949, 2816) discusses the somewhat similar case where treatment of the bright greenish-yellow base, 1-phenyl-4-indolo(3′ : 2′-3 : 4)quinoline (IV), which has a vinylogous relationship with the anhydronium base (VI), with acids gives a colourless cation owing to the formation of the normal aromatic structure of the indole and quinoline system but that the mono-methiodide and -ethiodide are buff-coloured, probably owing to a resonance hybrid. In the present case, however, the methiodide (V) like the other quaternary salt (VII) is colourless as would be expected. When the methiodide (V) was warmed on the water-bath with dilute sodium hydroxide a yellow gummy product was formed and 2-chloroethylamine was readily evolved. The unsubstituted quaternary salt (VII) did not undergo a similar change under these conditions but gave, as already described, the anhydronium base (VI). The cation of the monomethiodide (V) has also the resonance forms (VII, VII*a*, and VII*b*; R = Me), and the quaternary hydroxide can presumably give rise to the two possible pseudo-bases (IX and X; R = Me). In this case, owing to the lack of the necessary hydrogen on the nitrogen atom in the 1-position, (IX; R = Me) cannot readily lose water. The other pseudo-base form (X; R = Me), however, can give 2-chloroethylamine and a glyoxalinoquinolone.

The quaternary chloride (VII) readily condensed with morpholine or piperidine to give respectively the morpholino-derivative (III) already described and the analogous piperidino-compound.

Although four 4′ : 5′-dihydro-5′-ketoglyoxalino(3′ : 2′ : 1 : 2)quinolinium salts have been prepared by Harriman (U.S.P. 2,421,693; *Chem. Abstr.*, 1947, **41**, 6830) by the condensation of 2-aminoquinoline and the appropriate α-halogenated acyl halide, no properties or reactions of these compounds are given and no earlier reference to this ring system can be found. A parallel series of reactions has, however, been carried out with 2-(2-chloroethylamino)pyridine hydrochloride and its derivatives by Bremer (*Annalen*, 1935, **521**, 286) who found that this salt when warmed with strong alkali gave 4 : 5-dihydropyriminazole. The free base, 2-(2-chloroethylamino)pyridine, was isolated and gave a quaternary salt in the hot, but no properties or analyses for these two compounds are given. Of particular interest was the cyclisation of 2-(*N*-2-chloroethyl-*N*-ethylamino)-5-nitropyridine with potassium carbonate to a base which Bremer considers might be the pseudo-base (XI).

An attempt was made to prepare a 2 : 4-di(alkylaminoethylamino)quinoline by condensing 2 : 4-dichloroquinoline and diethylaminoethylamine in the presence of copper powder. Although a vigorous reaction took place no crystalline base or salt was obtained even after fractional extraction of the base with alkali (cf. Buchmann and Hamilton, *J. Amer. Chem. Soc.*, 1942, **64**, 1357).

Compounds (I), (II), (III), and (VII), and the piperidino-analogue of (III), when tested against *E. histolytica* by the method of Laidlaw, Dobell, and Bishop (*Parasitology*, 1928, **20**, 207) by Dr. J. D. Fulton of this Institute, had only slight amœbicidal action.

Experimental.

2 : 4-*Di*-(2-*hydroxyethylamino*)*quinoline* (I).—2 : 4-Dichloroquinoline (19·7 g., 1 mol.), prepared from 2 : 4-dihydroxyquinoline by the method of Buchmann and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**,

1357), and ethanolamine (30 c.c., 5 mols.) were heated in an oil-bath until the external temperature reached 110°. When the internal temperature reached 95—100° the two layers mixed and the temperature rose to 125°. The flask was then removed from the oil-bath and, when the internal temperature rose to 150°, the reaction was moderated by cooling the flask. The mixture was then heated for a further 20 minutes at 145° and poured into water (800 c.c.), and the yellow oil which separated dissolved by warming the mixture to 40°. The yellow solution was made alkaline by the addition of excess of 2*N*-sodium hydroxide, and the precipitated crystalline base was collected and crystallised from ethanol, (1 l.), separating in colourless needles (21 g.), m. p. 190—191° (Found : N, 16·6. Calc. for $C_{12}H_{17}O_2N_3$: N, 17·0%). A mixed m. p. with a specimen (m. p. 193°) supplied by Dr. H. King showed no depression. Treatment of the base with *N*-hydrobromic acid gave a *monohydrobromide* which separated from ethanol as clusters of prisms, m. p. 184° (Found : C, 47·9; H, 5·7. $C_{12}H_{17}O_2N_3$,HBr requires C, 47·6; H, 5·5%).

2 : 4-*Di*-(2-*chloroethylamino*)*quinoline Hydrochloride* (II).—The dihydroxy-base (24·7 g.) was added to phosphorus oxychloride (120 c.c.). After 1 minute a vigorous reaction started at room temperature, the mixture was vigorously shaken, and the flask plunged into cold water. When the reaction had subsided the clear solution was heated on a water-bath for 1 hour. The excess of phosphorus oxychloride was removed on the water-bath under reduced pressure and the syrupy residue poured into water (300 c.c.) and warmed slightly to facilitate decomposition of the complex. The mixture was left overnight at 0°. The solid was collected and crystallised from methanol–ethyl acetate from which the *hydrochloride* separated slowly in rosettes of long slender prisms (30 g.), m. p. 133° (Found : C, 46·2; H, 5·3; N, 12·4; Cl^-, 11·3; H_2O, 5·0. $C_{13}H_{18}N_2Cl_2$,HCl,H_2O requires C, 46·1; H, 5·3; N, 12·4; Cl^-, 10·8; H_2O, 5·3%). After being dried at 100° the anhydrous *hydrochloride* has m. p. 145° (Found : C, 48·95; H, 5·1. $C_{13}H_{18}N_2Cl_2$,HCl requires C, 48·7; H, 5·6%).

4′ : 5′-*Dihydro*-4-(2-*morpholinoethylamino*)*glyoxalino*(3′ : 2′-1 : 2)*quinolinium Chloride Hydrochloride* (III).—(*a*) The hydrochloride (II) (5 g.) and morpholine (15 c.c.) were heated on a water-bath for 30 minutes. The salt dissolved and after 15—20 minutes a heavy solid was precipitated. The mixture was cooled to 0°, ether was added, and the solid material collected and dissolved in slight excess of dilute hydrochloric acid. The solution was taken to dryness and the resulting solid gave after several recrystallisations from ethanol the quaternary *chloride hydrochloride* (2·5 g.) in sheathes of woolly needles, m. p. 290° (Found : C, 52·7; H, 6·95; N, 13·9; H_2O, 5·5. $C_{17}H_{25}ON_4Cl$,HCl,H_2O requires C, 52·4; H, 6·7; N, 14·4; H_2O, 4·6%). A specimen was analysed after drying at 115° for 5 hours (Found : C, 55·0; H, 7·0. $C_{17}H_{25}ON_4Cl$,HCl requires C, 55·0; H, 6·5%).

(*b*) Prepared in the same way as the piperidino-compound recorded below, from (VII) and morpholine, the salt separated from alcohol in needles, m. p. 290°, undepressed on admixture with that recorded in (*a*).

4-(2-*Chloroethylamino*)-4′ : 5′-*dihydroglyoxalino*(3′ : 2′-1 : 2)*quinolinium Chloride* (VII).—(*a*) To a suspension of 2 : 4-di-(2-chloroethylamino)quinoline hydrochloride (10 g.) in water (300 c.c.) was added a cold saturated solution of sodium hydrogen carbonate (250 c.c.). The pale yellow oil precipitated was rapidly extracted with ether (3 × 100 c.c.). If the free base is not extracted at once it cyclises spontaneously and dissolves in the aqueous solution. The filtered ethereal extract rapidly became cloudy and when kept at room temperature deposited colourless crystals. The there was distilled off and the resulting white solid was recrystallised from ethanol from which the quaternary *chloride* separated in long prisms (4·0 g.), m. p. 220—221° (Found : C, 52·1; H, 6·1; N, 14·3; Cl^-, 11·4; H_2O, 6·3. $C_{13}H_{18}N_2Cl_2H_2O$ requires C, 51·7; H, 6·3; N, 13·9; Cl^-, 11·7; H_2O, 6·0%). The salt was dried for analysis at 115° (Found : C, 55·3; H, 5·0; N, 14·3. $C_{13}H_{18}N_2Cl_2$ requires C, 54·9; H, 5·3; N, 14·8%). Treatment with excess of *N*-hydrochloric acid gave the quaternary chloride unchanged. An aqueous solution of the salt is unaffected by treatment with sodium hydrogen carbonate or sodium carbonate solution, but a yellow base is precipitated when 2*N*-sodium hydroxide is added (see below).

(*b*) The crude anhydronium base (VI) [see below ; from (II) (30 g.)] was treated with hot *N*-hydrochloric acid (75 c.c.), and the resulting solution was concentrated under reduced pressure. After cooling, the white crystalline mass (20 g.) was collected and crystallised from ethanol in long prisms (19·5 g.), m. p. 219—221°, identical with the chloride described above (mixed m. p.). Similar treatment with aqueous hydrogen bromide gave the corresponding *bromide* as colourless needles (from ethanol), m. p. 220° (Found : C, 47·4; H, 4·9; N, 12·8. $C_{13}H_{18}N_2ClBr$ requires C, 47·5; H, 4·6; N, 12·8%).

4-(2-*Chloroethylamino*)-4′ : 5′-*dihydroglyoxalino*(1′ : 2′-1 : 2)*quinoline* (VI).—(*a*) To a solution of 2 : 5-di-(2-chloroethylamino)quinoline hydrochloride (17 g.) in warm water (150 c.c.) was added 2*N*-sodium hydroxide (50 c.c.). The white oil, which separated, rapidly became yellow and, after warming of the mixture at 40° for 5 minutes, the yellow oil solidified. The mixture was cooled rapidly and the yellow *glyoxalinoquinoline* collected and crystallised from ethanol as bunches of fine yellow prisms or from ethyl acetate, in which it is only sparingly soluble, as stout yellow prisms, m. p. >320° (Found : C, 63·2; H, 5·8; N, 16·2. $C_{13}H_{14}N_3Cl$ requires C, 63·0; H, 5·65; N, 16·95%). The base, which gives a positive Beilstein test, gives with potassium dichromate and concentrated sulphuric acid a greyish-green colour which develops through reddish-brown to olive-green.

(*b*) The chloride (VII) (1·4 g.) in water (10 c.c.) was treated with 2*N*-sodium hydroxide (20 c.c.); the yellow oil which separated solidified on slight warming and scratching. The base (VI), when collected, washed with water, and dried, had m. p. <320°. Treatment with dilute hydrobromic acid gave the quaternary bromide, which separated from ethanol in colourless needles, m. p. 219°, and gave no depression of m. p. when admixed with the bromide described above.

1 : 4-*Bis*-[4′ : 5′-*dihydroglyoxalino*(1′ : 2′-1 : 2)*quinol*-4-*yl*]*piperazine* (XII).—The chloride (VII) (1·45 g.) in ethanol (50 c.c.) was kept in 2*N*-sodium hydroxide (2 c.c.) for several weeks at room temperature. After filtration, the yellow solution was evaporated to dryness under reduced pressure. The yellow solid residue was triturated with ether and filtered off. The *piperazine* separated from benzene in short stout yellow prisms, m. p. 167°; it does not melt sharply, and gradually forms a meniscus above 167° (Found : C, 73·9; H, 6·0; N, 19·7. $C_{26}H_{24}N_6$ requires C, 73·9; H, 6·1; N, 19·9%).

4-(2-*Chloroethylamino*)-4' : 5'-*dihydro*-1'-*methylglyoxalino*(3' : 2'-1 : 2)*quinolinium Iodide* (V).—Methyl iodide (0·28 g.) was set aside overnight at room temperature in a solution of (VI) (0·5 g.) in methyl alcohol. The long slender needles, m. p. 225—226°, which separated (0·3 g.), were recrystallised from methanol to give the colourless quaternary *methiodide*, m. p. 226° (Found: C, 42·7; H, 4·5; N, 10·9. $C_{14}H_{17}N_3ClI$ requires C, 43·1; H, 4·4; N, 10·8%).

Action of Dilute Alkali on the Methiodide (V).—The methiodide (V) (1·0 g.) was boiled with 2*N*-sodium hydroxide (15 c.c.) for 10 minutes and the basic vapour, which was readily evolved, was passed into dilute hydrochloric acid. The acid solution was taken to dryness under reduced pressure, and ethyl alcohol was added and then removed under reduced pressure, to give a colourless hygroscopic salt (0·03 g.). Aqueous sodium picrate was added to this and a yellow picrate in long needles, m. p. 140—141°, separated at 0°. Recrystallisation from a small amount of water gave 2-chloroethylamine picrate, m. p. 141—142°. A mixed m. p. with an authentic specimen (m. p. 142—143°) showed no depression (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914, gives m. p. 142—143°). No crystalline material has yet been obtaind from the yellow gummy product which remained in the distilling flask.

4' : 5'-*Dihydro*-4-(2-*piperidinoethylamino*)*glyoxalino*(3' : 2'-1 : 2)*quinolinium Bromide Hydrobromide*.—The chloride (VII) (2·8 g., 1 mol.) was heated on the water-bath with piperidine (10·9 c.c. 10 mols.) for 30 minutes. The salt gradually dissolved and after 15—20 minutes a red oil separated which gradually solidified on further heating to give a heavy yellow precipitate. The mixture was cooled to 0°, ether was added, and the solid collected and washed with ether. Treatment of the solid with *N*-hydrobromic acid (40 c.c.), evaporation to dryness under reduced pressure, and crystallisation from ethanol gave the *bromide hydrobromide* in colourless short needles, m. p. 292° (Found: C, 46·7; H, 5·8; N, 12·0. $C_{18}H_{23}N_4Br,HBr$ requires C, 47·2; H, 5·7; N, 12·2%). The *chloride hydrochloride* separated from ethanol in microcrystalline form, m. p. 295° (Found: C, 55·7; H, 7·3; N, 14·3; H_2O, 5·2. $C_{18}H_{23}N_4Cl,HCl,H_2O$ requires C, 55·8; H, 7·2; N, 14·5; H_2O, 4·7%).

Reaction between Diethylaminoethylamine and 2 : 4-*Dichloroquinoline*.—2 : 4-Dichloroquinoline (1·97 g., 1 mol.), 2-diethylaminoethylamine (6·9 g., 6 mols.), and copper powder (0·25 g.) were heated in an oil-bath. At 120° a vigorous reaction ensued and the mixture was then heated at 140° for a further 3 hours. The mixture was treated with dilute alkali and the bases were extracted with chloroform. The chloroform and excess of base were removed by distillation at 130° under reduced pressure. The remaining red gummy base could not be induced to crystallise or to give a crystalline salt. The base was fractionally extracted from *N*-hydrobromic acid (40 c.c.) with *N*-sodium hydroxide (4 × 10 c.c.) and chloroform in 10 fractions. No crystalline base or salt could be obtained.

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376. *The Dependence of Optical Rotatory Power on Chemical Constitution. Part XXXVII.** cyclo*Hexylphenylcarbinol.*

By MICHAEL P. BALFE, GILBERT H. BEAVEN, and JOSEPH KENYON.

The rotatory dispersions of *cyclo*hexylphenylcarbinol and of its acetate, formate, benzoate, and hydrogen phthalate in the visible spectrum, and their absorption spectra between 2100 and 2900 A., are recorded. The constants are given of one-term Drude equations which fit tolerably well the observed rotatory dispersions. It is suggested that induced anisotropy of phenyl chromophores has an observable effect in the rotatory powers of the acetate, formate, and benzoate, and not of the carbinol itself.

TABLE I summarises the ultra-violet absorption spectrum between 2100 and 2900 A. of *cyclo*hexylphenylcarbinol and some of its esters. In the carbinol, and its acetate, formate, and chloride, the absorption is due to the phenyl group, since the *cyclo*hexyl and hydroxyl groups and chlorine substituents are all effectively transparent down to about 1900 A. The absorption bands of these four compounds, in wave-lengths, extinction coefficients, and fine structures, are typical of the benzene chromophore containing a saturated substituent (cf. Braude, *Ann. Reports*, 1945, **42**, 124), the spectra being very similar to the absorption spectrum of benzyl alcohol, for which in ethanol, $\lambda_{max.}$ occurs at 2565 A. and $\varepsilon_{max.}$ is 178, with accompanying fine structure (*Tables Annuelles*, **13**, Part **33**, p. 61). In the benzoate and hydrogen phthalate, the presence of the second phenyl group, containing carboxyl and carbalkoxy-substituents, has moved the absorption bands to longer wave-lengths and increased $\varepsilon_{max.}$: in the benzoate four maxima remain in the zone of longer wave-length, but in the hydrogen phthalate this detail has been suppressed.

* Parts XXXIII, *J.*, 1928, 3000; XXXIV, *J.*, 1939, 633; XXXV, *J.*, 1941, 312; XXXVI, *J.*, 1942, 531.

TABLE I.

Ultra-violet absorption spectra of cyclo*hexylphenylcarbinol and its derivatives.*

Compound (solvent).	Short-wave band. $\lambda_{max.}$, A.	Short-wave band. ε_{molar}	Long-wave band. $\lambda_{max.}$, A.	Long-wave band. ε_{molar}
Carbinol (light petroleum)	*ca.* 2120	*ca.* 6550	2475	103
			2525	149
			2585	186
			2645	141
			2680	80
Acetate (light petroleum)	2155	3830	2470	141
			2520	171
			2580	207
			2640	165
Formate (light petroleum)	2110	8000	2478	121
			2520	164
			2580	209
			2640	166
Chloride (light petroleum)	*ca.* 2150	7420	2470	552
			2525	535
			2587	474
			2645	*328*
Benzoate (*n*-hexane)	2240	17,700	2595	765
			2665	780
			2740	883
			2815	795
Hydrogen phthalate (*cyclo*hexane)	2280	10,300	2780	1420

Italics denote an inflection.

TABLE II.

Rotatory dispersion of cyclo*hexylphenylcarbinol* (obs. = observed; calc. = calculated from Drude constants in Table IV).

Solvent.	Concn., g./100 c.c.	*t.*		$[\alpha]_\lambda$. λ, A. 6438.	5893.	5780.	5461.	4800.	4358.
Ethanol	9·715	19°	obs.	18·71	22·52	23·42	26·13	34·26	42·24
			calc.	18·71	22·45	23·47	26·37	34·53	42·24
Benzene	3·29	22	obs.	23·71	28·27	28·58	32·83	43·62	52·89
			calc.	23·63	28·27	29·50	33·20	43·48	53·37
Carbon disulphide	4·027	22	obs.	24·83	29·80	30·79	34·27	46·31	55·63
			calc.	24·74	29·71	31·00	34·77	45·66	55·83
*cyclo*Hexane	3·696	22	obs.	27·87	31·80	32·75	37·75	51·95	61·70
			calc.	27·20	32·70	34·03	38·30	50·13	61·50
Pyridine	3·687	22	obs.	27·40	31·61	33·10	37·58	50·46	62·13
			calc.	27·05	32·50	33·80	38·05	49·83	61·13
Ethyl ether	4·030	20	obs.	—	38·8	—	—	—	—
	15·63	20	obs.	—	37·6 •	—	—	—	—

• Levene and Mikeska, *J. Biol. Chem.*, 1927, **75**, 587.

Table II gives the rotatory dispersion of the carbinol in various solvents, and Table III the dispersion of the esters, each in one solvent. The signs of rotatory power have been omitted; it can be shown that the (+)-carbinol, (+)-acetate, (+)-formate, and (+)-(hydrogen phthalate), and the (−)-benzoate have the same relative configuration (Balfe, Beaven, and Kenyon, in preparation). The data for the chloride refer to the preparation of highest rotatory power, and for the carbinol and esters to optically pure preparations.

Specific rotatory powers at λ_{4358} of the carbinol and esters in a number of other solvents can be calculated from concentrations and initial observed rotatory powers (some extrapolated to zero time) which will be given in kinetic data by Balfe, Beaven, and Kenyon.

The one-term Drude equation derived from the rotatory powers of the carbinol in ethanol solution gives calculated values of rotatory power which are in good agreement with the observed. Extrapolated straight-line plots of $1/\alpha$–λ^2 in the other solvents cut the λ^2 axis at values close to the λ_0^2 in this equation. This value for λ_0 (*i.e.*, 1070 A.) was therefore assumed

for the data in other solvents, and values for k were calculated thereform. The resulting equations give calculated [α] values which are in tolerable agreement with the observed results; calculation of constants from the observed results by the usual method (Lowry, "Optical Rotatory Power," London, 1935, p. 420) did not give better-fitting equations. For the hydrogen phthalate, acetate, formate, and benzoate in ethanol, one-term Drude equations were calculated which fit reasonably well the observed results. Neither a one-term nor a two-term, three-constant equation could be derived for the dispersion data of the hydrogen phthalate in chloroform, either by the usual method of calculation (Lowry, *op. cit.*) or by successive approximations from selected values for the constants.

TABLE III.

Rotatory dispersion of esters of cyclo*hexylphenylcarbinol* (obs. = observed; calc. = calculated from Drude constants in Table IV).

Ester.	Solvent.	Concn., g./100 c.c.	l.		λ, A. 6438.	5893.	5780.	5461.	4800.	4358.
Acetate	Ethanol	3·984	20°	obs.	57·9	71·0	73·4	84·2	118·0	147·1
				calc.	57·8	70·8	73·9	84·2	115·2	147·9
Formate	Ethanol	2·307	18	obs.	60·2	75·4	—	90·6	123·1	163·6
				calc.	61·5	75·4	79·0	91·0	126·0	163·6
Benzoate	Ethanol	2·083	28	obs.	25·5	32·2	33·9	40·1	60·0	83·5
				calc.	25·5	32·2	33·9	39·8	59·3	83·5
Hydrogen phthalate	Ethanol	4·085	21	obs.	18·0	21·9	22·4	25·7	—	41·6
				calc.	18·3	21·9	22·9	25·7	33·8	41·6
	Chloroform	2·22	16	obs.	38·9	51·8	55·4	64·0	87·9	113·5
		4·00	20	obs.	—	52·5 *	—	—	—	—
Chloride	Ethyl ether	9·6	20	obs.	—	62·0	—	—	—	—
		9·89	20	obs.	—	29·4 *†	—	—	—	—

* Levene and Mikeska, *loc. cit.* (Table II).
† From carbinol of about half the maximum rotatory power.

TABLE IV.

Constants of one-term Drude equations, lowest λλ *of absorption, dispersion ratios, and plot of* $1/\alpha - \lambda^2$.

	Carbinol.	Acetate.	Formate.	Benzoate.	Hydrogen phthalate.	
Drude constants, k	14·35, 18·065, 18·977, 20·835, 20·699 *	49·356 §	48·067 §	24·195 §	24·637 §	indeterminate **
λ_0, A.	1070 †	2145 §	2353 §	3025 §	1224 §	
λ (A.) of main absorption maxima (Table I)	2120 ‡ 2585 ‡	2155 ‡ 2580 ‡	2110 ‡ 2580 ‡	2240 ‖ 2740 ‖	2280 ¶ 2780 ¶	
Dispersion ratios	1·62, 1·61, 1·62, 1·63, 1·65 *	1·75 §	1·80 §	2·08 §	1·62 §	1·77 *
Plot of $1/\alpha - \lambda^2$	linear †	linear §	linear §	linear §	linear §	concave to $1/\alpha$ axis **

* In ethanol, benzene, carbon disulphide, *cyclo*hexane, and pyridine, in that order.
† In all solvents. ‡ In light petroleum. § In ethanol.
‖ In *n*-hexane. ¶ In *cyclo*hexane. ** In chloroform.

The plots of $1/\alpha$–λ^2 for the carbinol in the various solvents, and for the acetate, formate, and hydrogen phthalate, are straight lines, suggesting that $\lambda_2 < \lambda_0 < \lambda_1$ (Levene and Rothen, in Gilman's "Organic Chemistry," 1st Edn., New York, 1938, p. 1800: λ_0 being the characteristic frequency of the one-term Drude equation which fits the observations in the visible spectrum, and λ_1, λ_2 the characteristic frequencies of the two-term equation which would presumably be required to fit observations of the dispersion extended through the visible to the near ultra-violet): λ_0 is thus a lower limit to λ_1. In the carbinol, λ_0 (1070 A.) is so far below the short-wave absorption bands (*ca.* 2100 A.) associated with the phenyl chromophores (see Table IV), that it seems probable that λ_1 would be derived not from these, but from anisotropy in the C–OH group which has its first absorption region located near 1800 A. The dispersion ratios for the carbinol fall in a range which is consistent with "simple" dispersion, *i.e.*, a one-term equation covering the dispersion in the whole of the accessible spectrum: λ_0 (1070 A.) is the characteristic frequency

in this equation. Though similar considerations apply to the comparison of λ_0 (in ethanol) and the observed absorption bands of the hydrogen phthalate, the difference between its dispersion ratios in two solvents, and the high values of the dispersion ratio in chloroform, make it unlikely that a one-term equation would fit the dispersion in the ultra-violet spectrum: in a two-term equation, λ_1 is less likely, than it is in the carbinol, to be the C·OH chromophore at 1800—2000 A., and may be associated with the phenyl chromophores. In the acetate and formate, the dispersion ratios suggest that a two-term equation would be required for the full dispersion range. Comparison of λ_0 and the wave-lengths of the absorption bands suggests that λ_1 could be associated with the phenyl absorption bands, λ_2 being again probably at about 1800 A. Although the $1/\alpha$–λ^2 plot for the benzoate is a straight line (Table IV), λ_0 (3025 A.) cannot be a lower limit for λ_1, since this would place λ_1 in the violet or near ultra-violet and it is most improbable that in such a case $1/\alpha$–λ^2 for the visible spectrum would be a straight line. It is more likely that the dispersion equation involves two terms of opposite sign:

$$[\alpha]_\lambda = \frac{k_1}{\lambda^2 - \lambda_1^2} - \frac{k_2}{\lambda^2 - \lambda_2^2}$$

The dispersion ratio for the benzoate also suggests that a two-term equation would be necessary, and in this case λ_1 might well be associated with the phenyl chromophore.

The suggestions put forward then are as follows:

(i) In the carbinol, anisotropy in the phenyl group does not make an observable contribution to the rotatory power; its absorption spectrum is only slightly affected by the introduction of the $\cdot CH(OH)\cdot C_8H_{11}$ substituent.

(ii) In the acetate and formate, the effect of the phenyl group on the rotatory power becomes apparent: this group is rendered capable of anisotropic absorption by vicinal action between the phenyl and ester-carbonyl groups; the interaction is trivial (cf. Kuhn, *Trans. Faraday Soc.*, 1930, **26**, 293), as shown by the small increases in extinction coefficients.

(iii) The benzoate contains a second phenyl group which is attached to the polarisable ester-carbonyl group. The phenyl absorption bands are now shifted to longer wave-lengths and their absorption coefficients still further increased: the contribution from the benzoate radical predominates over the similar but less intense contribution from the phenyl group in the carbinol (cf. Braude, *loc. cit.*, p. 126). A new Drude term is introduced by vicinal action in this second phenyl chromophore and is probably opposite in sign to the shorter-wave-length term, as is indicated by the necessity for assuming terms of opposite sign in the dispersion equation, and by the difference in sign of rotatory power between the benzoate on the one hand, and the carbinol and other esters of the same configuration on the other.

(iv) In the hydrogen phthalate, the intense contribution of the phthalate chromophore dominates the absorption spectrum (cf. "A.P.I. Ultraviolet Absorption Spectrograms," Serial Nos. 101—103, U.S. Bureau of Standards, 1945), and the presence of the second phenyl chromophore complicates the rotatory dispersion.

Experimental.

The preparation of the optically active carbinol and esters will be described by Balfe, Beaven, and Kenyon (see also Levene and Mikeska, *loc. cit.*).

Absorption spectra were determined in spectroscopic-grade solvents, using (i) Hilger "medium" quartz spectrograph with "Spekker" or sector UV photometers and high-frequency tungsten spark under water or condensed spark between tungsten-steel electrodes, (ii) Beckman photo-electric quartz spectrophotometer and hot-cathode hydrogen arc source.

Rotatory powers were determined at room temperature in 2-dm. tubes.

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377. *The Dependence of Optical Rotatory Power on Chemical Constitution. Part XXXVIII. (−)-1-Chloro-3-phenoxypropan-2-ol and (−)-Glycide Phenyl Ether.*

By Michael P. Balfe, Michael K. Hargreaves, and Joseph Kenyon.

The hydrogen phthalate of (−)-1-chloro-3-phenoxypropan-2-ol is an intermediate in the preparation of (−)-glycide phenyl ether. The (−)-alcohol was prepared to check the optical purity of the ether. Rotatory powers of the (−)-alcohol and its hydrogen phthalate are recorded.

The rotatory dispersions of the homogeneous (−)-glycide phenyl ether, between 6708 and 3180 A., and of solutions in a variety of solvents, in the visible spectrum, are recorded. Drude equations cannot be derived solely from the experimental results, but a number of two-term equations and one of three terms for the homogeneous ether, and a three-term equation (but none with two terms) for the solution in ethyl ether can be calculated for assumed characteristic wave-lengths which are in part derived from the absorption spectrum.

The rotatory powers and dispersion characteristics of the ether are very sensitive to changes of temperature or of solvent: increase of temperature, and dissolution in ethereal solvents, result in the lowest rotatory power. The rotatory dispersion is most complex in ethereal solutions. It is suggested that these observations can be explained by assuming molecular association in the homogeneous substance, which is lessened by increase of temperature or dissolution in ether.

1-Chloro-3-phenoxypropan-2-ol was prepared as described by Boyd and Marle (*J.*, 1910, **97**, 1788) and converted into the hydrogen phthalate by the usual method. The (−)-ester was obtained by recrystallisation of its brucine salt. Hydrolysis of the (−)-ester with potassium hydroxide yields (−)-glycide phenyl ether, $Ph{\cdot}O{\cdot}CH_2{\cdot}\underset{O}{\overset{\diagup\diagdown}{CH}}{-}CH_2$, which on treatment with hydrochloric acid yields (−)-1-chloro-3-phenoxypropan-2-ol; the (−)-(hydrogen phthalate) prepared from this alcohol has the same rotatory power as that from which the ether was prepared, indicating that no racemisation occurs at any of the stages of preparation.

Table I summarises the absorption spectrum of glycide phenyl ether, $CH_2{\cdot}\underset{O}{\overset{\diagup\diagdown}{CH}}{\cdot}CH_2{\cdot}OPh$, which is dominated by the absorption of the phenyl chromophore, and shows the usual effects of substitution on the absorption spectrum of benzene, *viz.*, some loss of vibrational fine structure, displacement to longer wave-lengths, and an increase in intensity of the long-wave band.

Table I.

The ultra-violet absorption spectrum of glycide phenyl ether.

(1) *In mixed octanes.*

$\lambda_{max.}$, A.	2770	2705	2650	2195
$\varepsilon_{max.}$	1520	1740	1230	7480

(2) *Homogeneous.* No *selective* absorption down to 2940 A. For a layer of 0·10 cm. the optical density rises smoothly from 0·05 at 3100 A. to 0·78 at 2940 A., corresponding to a molar extinction coefficient of about 0·5, *i.e.*, of the same order as in octane solution at this wave-length.

Table II.

Specific rotatory powers of (−)-glycide phenyl ether, homogeneous.

t, 18·5°; *l*, 0·5:

λ.	6708.	6438.	6107.	5893.	5780.	5461.	5086.	4800.	4678.	4358.
[α], obs. ...	18·5°	20·2°	22·9°	24·9°	25·5°	28·2°	32·9°	37·2°	38·6°	45·6°
[α], calc. ...	18·1°	—	—	—	—	28·2°	—	—	—	46·5°

t, 18°; *l*, 0·25:

λ.	4707.	4647.	4630.	4602.	4556.	4528.	4476.	4461.	4415.	4383.	4337.	4285.	4260.	4202.
[α], obs.	38·9°	39·1°	39·6°	40·4°	41·3°	42·2°	43·1°	44·0°	44·9°	45·8°	46·7°	47·6°	48·5°	49·4°

t, 18·5°; *l*, 0·05:

λ.	4346.	4088.	3873.	3603.	3485.	3394.	3292.	3180.
[α], obs.	46·8°	52·3°	57·7°	68·2°	73·7°	78·9°	84·4°	89·7°
[α], calc.	—	—	—	71·3°	—	—	84·4°	87·0°

Table II gives the specific rotatory powers of homogeneous (−)-glycide phenyl ether in visible and ultra-violet light, down to the limit of transmission. The plot of $1/\alpha-\lambda^2$ is a

straight line, except for the three points below λ 3300 A. One-term Drude equations can be calculated from a variety of pairs of points in the dispersion (α–λ) curve, but the resulting λ_0's vary somewhat widely, and if points lying within less than 300 A. of each other on the wave-length scale are used for the calculation, the λ_0 values pass through a minimum as the wave-lengths of the points used pass along the wave-length scale, suggesting that there is an inflection in the α–λ plot. It therefore appears that a two-term equation would be required to fit the observed results satisfactorily. We have not been able to calculate a two-term equation from any four points read from a smooth curve drawn through α–λ. We have, however, been able to derive several equations which fit tolerably well the observed results, by assuming values of λ_1 and λ_2 and calculating k_1 and k_2 from two of the observed points. Calculated values of $[\alpha]_\lambda$ from one such equation,

$$[\alpha]_\lambda = \frac{0{\cdot}763}{\lambda^2 - 0{\cdot}0795} - \frac{8{\cdot}415}{\lambda^2 - 0{\cdot}0324}$$

are given in Table II. All the equations so derived are consistent with the idea that one of the absorption bands of the phenyl chromophore, and one in the experimentally inaccessible region below 1900 A., are optically active. A three-term equation

$$[\alpha]_\lambda = \frac{-1{\cdot}334784}{\lambda^2 - 0{\cdot}0795} + \frac{2{\cdot}047924}{\lambda^2 - 0{\cdot}0729} - \frac{8{\cdot}772339}{\lambda^2 - 0{\cdot}0169}$$

has also been fitted to the results. This was derived by starting with the 2770 and 2650 A. maxima in the absorption spectrum as characteristic frequencies for the first two terms, and 1300 A. for the third term. The first two frequencies were then increased, in accordance with the frequently observed relation $\lambda_0 - \lambda_{max.} \sim 100$ A. (Lowry, "Optical Rotatory Power," London, 1935, pp. 145, 146) until an equation to fit the observed results was obtained: λ_1 and λ_2 in the equation given above correspond to characteristic frequencies of 2830 and 2700 A. This procedure has a practical justification in that the calculation of the three-term equation involves the use of an additional experimental observation, and so results in a somewhat better fit to the observations. There cannot be any physical significance in the separation, in the dispersion equation, of two terms with characteristic frequencies which are fine-structure (vibrational) maxima in the absorption band of a single electronic excitation process: the first two terms of this equation must be regarded as arising from difficulties in computation and as together covering the contribution to the rotatory power from anisotropy in the phenyl chromophore.

Table III gives the rotatory dispersion of (−)-glycide phenyl ether in ethyl ether solution. We have not been able by any method to derive a one- or two-term equation to fit these results. A three-term equation

$$[\alpha]_\lambda = \frac{40{\cdot}122936}{\lambda^2 - 0{\cdot}0795} + \frac{50{\cdot}901337}{\lambda^2 - 0{\cdot}729} - \frac{14{\cdot}482839}{\lambda^2 - 0{\cdot}0169}$$

can be derived by assuming the same three wave-lengths as above, and this fits a smooth curve of α–λ within the scatter of the observed points.

TABLE III.

Specific rotatory powers of (−)-glycide phenyl ester in diethyl ether solution.

t, 19·6°; *c*, 10·32; *l*, 1·0 above, and 0·5 below λ 4000.

λ.	6438.	5893.	5780.	5461.	5086.	4800.	4358.	3998.	3983.
[α]	7·2°	8·3°	8·7°	9·6°	10·5°	11·1°	12·3°	13·0°	14·5°
λ.	3937.	3907.	3843.	3813.	3756.	3680.	3545.		
[α]	16·0°	17·4°	18·95°	23·3°	24·8°	30·6°	38·0°		

Table IV gives the rotatory powers of (−)-glycide phenyl ether in a variety of solvents, in the visible spectrum. The variations are greater than can be accounted for by variations in the refractive indices of the solutions since the rotivities ($\Omega = 3[\alpha]/(n^2 + 2)$; Beckman and Cohen, *J. Chem. Physics*, 1936, **4**, 784; 1938, **6**, 163) vary over almost as wide a range as the specific rotatory powers.

Table V gives the rotatory power of homogeneous (−)-glycide phenyl ether, at temperatures from 25° to 174°. The effect of increase in temperature on the rotatory power is exceptionally great. In di-*n*-butyl ether solution (Table IV) the temperature effect is even greater, and the characteristics of anomalous rotatory dispersion, *i.e.*, inflection, maximum, and change of sign of rotation, are evident, moving towards longer wave-lengths as the temperature is increased;

the first two are apparent in the red and the blue region of the spectrum at 41°, at 80° they have disappeared and the third is evident in the green.

TABLE IV.

Specific rotatory powers of (−)-glycide phenyl ether in various solvents.

				Wave-length, A.									
Solvent.	*l*.	*c*.	Temp.	6708.	6438.	6104.	5893.	5780.	5461.	5086.	4800.	4358.	$[\alpha]_{5461}^{4358}$ / $[\alpha]_{5461}$	Ω_D.
Carbon disulphide	0·5	15·0	17°	—	18·8°	—	22·7°	—	27·7°	32·3°	37·1°	47·1°	1·70	14·8
Pyridine	1·0	5·2	16	17·9°	19·2	21·7°	22·6	24·6°	27·3	31·7	34·6	43·6	1·60	15·8
Benzene	1·0	10·3	21	16·6	18·3	20·3	21·9	23·0	25·7	30·1	34·3	42·4	1·65	15·5
Methyl alcohol	0·5	10·0	17	—	16·7	—	20·3	21·6	24·3	28·2	30·2	35·4	1·49	15·9
Nitromethane	1·0	9·2	20	12·7	14·4	15·8	17·7	18·6	20·6	23·3	25·6	30·1	1·48	13·5
Acetone	0·5	9·4	19	—	12·3	—	16·2	17·9	19·7	23·6	25·9	27·8	1·41	12·5
,,	0·5	36·0	17	—	15·1	—	—	20·5	24·0	27·1	29·4	34·8	1·45	—
Ethyl alcohol	1·0	8·1	18	10·3	11·5	13·1	14·1	14·5	16·4	19·1	20·7	24·9	1·52	10·9
n-Propyl chloride	1·0	12·9	19	9·6	10·1	11·1	12·0	13·1	14·3	15·4	16·4	19·8	1·37	9·1
Diethyl ether	0·5	18·4	17	—	—	—	11·6	11·9	14·4	14·6	—	19·2	1·33	8·9
,,	1·0	13·0	20	—	7·2	—	8·3	8·7	9·6	10·5	11·1	12·2	1·27	6·4
,,	1·0	13·0	17	—	7·9	—	9·1	9·5	10·5	11·6	12·4	13·6	1·30	7·0
Di-*n*-propyl ether	1·0	9·6	19	—	7·8	—	9·6	10·1	11·4	11·9	12·8	14·9	1·30	—
Diisopropyl ether	1·0	10·0	21	—	6·6	—	8·3	8·4	9·1	10·0	10·6	11·0	1·26	—
1 : 4-Dioxan	1·0	9·1	20	—	6·7	—	8·2	9·0	10·0	10·8	11·8	13·5	1·35	6·1
,,	0·5	32·0	17	—	—	—	—	—	16·4	—	—	25·0	1·52	—
Di-*n*-amyl ether	1·0	11·2	21	—	5·9	—	8·1	8·5	9·5	10·0	—	11·0	1·16	—
Di-*n*-butyl ether	1·0	9·4	22	—	5·3	—	—	6·9	7·6	7·8	—	8·4	1·15	—

Ω_D homogeneous = 16·9. Dispersion ratio, homogeneous = 1·62.

TABLE V.

The effect of temperature on the specific rotatory power of homogeneous (−)-glycide phenyl ether (l, 0·5).

	Specific rotatory powers at λ (A.).							
Temp.	6438.	5780.	5461.	5086.	4800.	4358.	$[\alpha]_{5461}^{4358}$ / $[\alpha]_{5461}$	d_4.
23·5°	19·5°	24·9°	26·8°	31·3°	35·3°	43·6°	1·62	1·106
42·8	16·7	20·8	23·5	27·0	—	37·2	1·58	1·093
61·0	14·1	17·8	19·8	22·8	26·0	31·3	1·58	1·079
80·0	11·8	15·0	16·7	19·6	21·8	26·0	1·55	1·064
98·0	10·4	12·7	14·3	16·4	18·4	21·8	1·53	1·051
141	—	7·9	8·3	—	—	11·9	1·42	1·018
174	—	5·3	5·5	—	—	6·8	1·24	0·993

In secondary carbinols with simple rotatory dispersion (Pickard and Kenyon, *J.*, 1911, **99**, 45; 1912, **101**, 620; 1913, **103**, 1923), and in camphor (Gore and Lowry, *Proc. Roy. Soc., A*, 1932, **135**, 22), an increase in temperature of 100° decreases the rotatory power by some 20%, and in (−)-menthol, the effect is even less (Pickard and Kenyon, *J.*, 1915, **107**, 35). In substances which do not undergo a change in molecular configuration with increase of temperature, a decrease in rotatory power of this magnitude is to be expected, on account of the decrease in refractive index, which appears in the numerator of the quantum-mechanical expression for rotatory power (Born and Jordan, "Elementare Quantenmechanik," 1930, p. 250) and on account of increased freedom of rotation about single bonds (Kauzmann, Walter, and Eyring, *Chem. Reviews*, 1940, **26**, 377). In compounds with rigid ring structures, the latter effect will not operate, as indicated by (−)-menthol. The powerful effect of temperature on the rotatory power of (−)-glycide phenyl ether may therefore be an indication that a change in the molecular species occurs on increase of temperature. Such a change is also the most likely cause of the wide variation in rotatory powers in different solvents. This variation does not appear to be

an effect of the electrostatic field of the solvent in the optically active molecule, since it apparently is not related to the dielectric constant of the solvent. It is not likely to be caused by combination of the solvent with the solute (which could alter the rotatory power by forming a new species of optically active substance, *i.e.*, imparting anisotropy to a previously optically inactive absorption band) because such combination would be lessened by increase in temperature, and so the dispersion should become more like that of the homogeneous substance on raising the temperature of the solution, whereas the dispersion in *n*-butyl ether solution at various temperatures (Table VI) indicates that the contrary is the case. It is also not caused by a large shift in the position of the long-wave band of the optically active ether in solution; solvents modify the fine structure of absorption bands, but do not cause a shift such as would account for their effects on the rotatory dispersion of glycide phenyl ether.

TABLE VI.

The effect of temperature on the specific rotatory power of (−)*-glycide phenyl ether in* n*-butyl ether solution* (c, 9·4; l, 1·0).

	Specific rotatory powers at λ (A.).					$[\alpha]_{4358}$,
Temp.	6438.	5780.	5461.	5086.	4358.	$[\alpha]_{5461}$
22°	−5·3°	−6·9°	−7·6°	−7·7°	−8·4°	1·105
41	−3·2	−3·8	−4·3	−5·3	−4·1	0·953
81	−2·4	−1·1	—	—	+1·9	—
96	−1·3	−0·7	+0·3	—	+3·2	11·8

TABLE VII.

Specific rotatory powers of phenyl (−)*-sec.-butyl ether in the homogeneous state and in solution in various solvents.*

				λ, A.							$[\alpha]_{4358}$,
Solvent.	*l.*	*c.*	*t.*	6438.	5893.	5780.	5461.	5086.	4800.	4678.	4358.	$[\alpha]_{5461}$
None (homogeneous)	0·25	—	18°	29·3°	36·0°	37·7°	42·1°	51·0°	59·4°	62·3°	74·9°	1·78
Diethyl ether	1·0	9·1	19	28·3	34·2	36·2	41·2	50·1	57·2	61·0	73·9	1·78
(±)-Propylene oxide	1·0	5·1	16	28·2	35·5	38·4	43·4	50·7	—	—	77·4	1·78

Aliphatic ethers of octan-2-ol (Kenyon and McNicol, *J.*, 1923, **123**, 14) and of benzylmethylcarbinol (Phillips, *J.*, 1923, **123**, 22) have simple rotatory dispersions in the visible spectrum, and their rotatory powers are much less sensitive than those of glycide phenyl ether to change in temperature or solvent, being reduced by not more than 50% by a 100° increase of temperature. The rotatory powers of the *n*-alkyl ethers of nonan-3-ol (which exhibits complex rotatory dispersion in the visible spectrum, Kenyon and Barnes, *J.*, 1924, **125**, 1395), undergo a similar reduction on increase of temperature. It therefore appears that the extreme sensitivity to temperature changes which is shown in the rotatory power of glycide phenyl ether is not a general characteristic of optically active ethers; and sensitivity to solvent changes is not a characteristic of phenyl ethers in particular, since the results in Table VII indicate that the rotatory power of phenyl *sec.*-butyl ether is comparatively insensitive to changes in solvent. It therefore appears that these sensitivities in glycide phenyl ether are connected with the presence of the ethylene oxide groups. They may be due to some form of molecular association at ordinary temperature in the homogeneous substance, which is lessened by increase of temperature or by dissolution in ethereal solvents. At ordinary temperatures the rotatory power of the homogeneous ether is controlled by optically active absorption bands at about 2700—2800 and 1300 A., the 1300-A. band being dominant in the visible region. At elevated temperatures or in ethereal solutions, the association is lessened, resulting in a relative increase in the contribution of the phenyl chromophore (*i.e.*, the term at about 2700—2800 A.) to the rotatory power, so that the dispersion becomes more complex. This increase is indicated by comparison of the two three-term equations given above: dissolution in ethyl ether increases k_1 and k_2 (associated with the phenyl chromophore) more than k_3 (associated with the high-frequency chromophore). The dispersion of the homogeneous ether becomes more complex at elevated temperatures, as shown by the decrease in dispersion ratios to 1·24 at 174° (Table V), and the combined effect of dissolution in an ethereal solvent and increase in temperature is even more pronounced (Table VI). These suggestions imply that the association involves the ethylene oxide ring, and that the oxygen atom of ethereal solvents can displace the association.

The rotatory power of phenylbenzylcarbinol (Gerrard and Kenyon, *J.*, 1928, 2564) is as

sensitive as that of glycide phenyl ether to increase of temperature or to solvent effects, which suggests that a similar discussion, involving association through the hydroxyl group, may be applicable to the structure of the carbinol.

Experimental.

1-Chloro-3-phenoxypropan-2-ol.—From phenol (376 g.), epichlorohydrin (370 g.), sodium hydroxide (2 g.), and water (20 c.c.), 364 g. of the redistilled alcohol, b. p. 134—136°/6 mm., were obtained, together with a few g. of glycerol αα'-diphenyl ether, m. p. 80° (Boyd and Marle, *J.*, 1909, **95**, 1807, give m. p. 80°) (Found : C, 73·4; H, 6·4. Calc. for $C_{15}H_{16}O_3$: C, 73·7; H, 6·6%).

1-Chloro-3-phenoxypropan-2-ol (270 g.) was added to a warm solution of phthalic anhydride (222 g.) in pyridine (132 g.). After 10 days at room temperature the mixture was dissolved in acetone and poured into cold dilute hydrochloric acid. The precipitated inactive ***hydrogen phthalate*** was filtered off, dissolved in ether, extracted with sodium hydrogen carbonate solution, precipitated with hydrochloric acid, dissolved in ether, dried ($CaCl_2$), and precipitated (436 g.) from the concentrated solution by addition of light petroleum. On recrystallisation from ether–light petroleum the ester was obtained as colourless plates, m. p. 97—98° (Found, by titration with 0·1N-sodium hydroxide : equiv., 335. $C_{17}H_{15}O_5Cl$ requires equiv., 334·5). If the reaction mixture is dissolved in toluene, instead of in acetone as above, the ester crystallises with m. p. 97° when the solution is poured into hydrochloric acid.

Dry brucine (788 g.) was dissolved in a solution of the hydrogen phthalate (669 g.) in dry ethyl acetate. The brucine salt (m. p. 108—110°) which crystallised during 2 weeks was recrystallised 4 times from ethyl acetate and then 5 times from acetone (brucine hydrogen phthalate was filtered off from each solution); the final (tenth) crop weighed 44 g. The ninth and the tenth crops yielded hydrogen phthalate with the same rotatory power ($[\alpha]_D^{17}$ −12·2° in ethyl ether), suggesting that the resolution was complete.

Ice-cold hydrochloric acid was poured into a mixture of the brucine salt of the above (−)-(hydrogen phthalate) and acetone. The (−)-ester separated and was extracted with ether; the solution was washed with dilute hydrochloric acid, and extracted with sodium hydrogen carbonate solution, from which the (−)-(hydrogen phthalate) was precipitated by addition of hydrochloric acid. The ester was extracted with ether, washed with water and dried (Na_2SO_4). On removal of the ether under reduced pressure, the (−)-ester remained as an uncrystallisable viscous liquid. Rotatory powers are in the Table. From a concentrated solution, in ether, of the hydrogen phthalate obtained from brucine salt which had been only twice recrystallised, ester of low rotatory power ($[\alpha]_D^{17}$ −6·0° in ether) crystallised, leaving in solution, ester with $[\alpha]_D^{17}$ −10·5° (*i.e.*, 85% of the maximum rotatory power).

Specific rotatory powers of (−)-1-*chloro*-3-*phenoxy*-2-*propyl hydrogen phthalate* (l = 2).

Solvent.	*c.*	Temp.	λ, A. 6438.	5893.	5780.	5461.	5086.	4800.	4358.	$[\alpha]_{5461}/[\alpha]_{5461}$
Ethyl ether	9·6	17°	−10·0°	−12·2°	−13·3°	−15·2°	−17·7°	−21·5°	−28·7°	1·89
Carbon disulphide	11·7	18	1·7	2·2	2·3	2·7	4·4	—	5·5	2·04
Acetone	11·8	18	5·2	6·6	7·2	8·1	9·9	11·3	15·4	1·90
Chloroform	13·2	19	4·1	4·8	4·9	5·8	7·7	—	9·9	1·70
Pyridine	11·4	20	0·48	0·53	—	0·75	—	—	—	—
Benzene	11·6	17	—	1·1	—	—	—	—	—	—

(−)-Glycide Phenyl Ether.—The lævorotatory hydrogen phthalate was hydrolysed to glycide phenyl ether by steam-distillation of 5-g. portions from 12·5N-potassium hydroxide (5 c.c.); with weaker alkali the hydrolysis was incomplete, and with larger proportions of 12·5N-alkali larger proportions of undistillable by-products were obtained. The distillate was extracted with ether; the extract was dried and, after removal of the ether, (−)-glycide phenyl ether was distilled; it had b. p. 133°/23 mm., n_D^{17} 1·5310, d_4^{20} 1·106, d_4^{30} 1·049 (2·0 g. from 10 g. of the hydrogen phthalate) (Found : C, 71·95; H, 6·7. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%). Rotatory powers are given in the following paper. (±)-Glycide phenyl ether has been described by Boyd and Marle (*J.*, 1908, **93**, 838) and Rider and Hill (*J. Amer. Chem. Soc.*, 1930, **52**, 1521).

(−)-1-Chloro-3-phenoxypropan-2-ol.—(−)-Glycide phenyl ether (6·5 g.) was shaken for 30 minutes with concentrated hydrochloric acid (6 c.c.) in cold water (6 c.c.). An ethereal extract from the mixture was washed 3 times with aqueous sodium hydroxide (0·1 mol.), then with water, dried (Na_2SO_4), and concentrated. (−)-1-Chloro-3-phenoxypropan-2-ol (7 g. from 15 g. of the ether) was obtained on distillation of the residue, with b. p. 143—5°/20 mm., n_D^{17} 1·5378. (−)-Glycide phenyl ether, $[\alpha]_D^{17}$ −24·4°, gives (−)-1-chloro-3-phenoxypropan-2-ol of $[\alpha]_D^{17}$ −2·1°, and the alcohol yields, by the method described above, (−)-(hydrogen phthalate) with the same rotatory power as the phthalate from which the ether was prepared.

Phenyl (+)-*sec.*-butyl ether was prepared from (+)-*sec.*-butyl alcohol with $[\alpha]_{5461}^{17}$ +10·9°. The alcohol (5 g.) was saturated with dry hydrogen bromide, heated under reflux for 1 hour, washed with concentrated sulphuric acid to remove butenes and with sodium hydrogen carbonate solution, and dissolved in ether. The solution was dried (Na_2SO_4) and concentrated. The residue of *sec.*-butyl bromide (3 g.) distilled at 80—86°. It was heated for 12 hours with freshly prepared sodium phenoxide (2·75 g.) for 12 hours; the mixture was then extracted with ether, the extract was washed with 3N-sodium hydroxide, dried ($CaCl_2$), and concentrated. Phenyl *sec.*-butyl ether (0·85 g.) distilled from the residue, with b. p. 75—76°/10 mm., n_D^{18} 1·4978, d_4^{18} 0·9350, $[\alpha]_D^{18}$ +28·34°. Sprung and Wallis (*J. Amer. Chem. Soc.*, 1934, **56**, 1715) give b. p. 84—85°/14 mm., n_D^{20} 1·4926, $[\alpha]_D^{20}$ +30·02°. Since the *sec.*-butyl alcohol was not optically pure the rotatory powers of the ether given in Table VII have been multiplied by 13·87/10·9, to bring them to the values for ether prepared from optically pure alcohol; these values,

however, cannot be regarded as the rotatory powers of optically pure ether, as there was probably some racemisation during the preparation of the bromide.

Rotivities Ω were calculated from $\Omega = 3[\alpha]/(n^2 + 2)$, by using the weighted means of refractive indices of solvents and solute.

The absorption spectrum was determined by Dr. G. H. Beaven using a Beckman photo-electric quartz spectrophotometer and hot-cathode hydrogen discharge. Thanks are expressed to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries Limited for grants, and to Professor R. G. W. Norrish, F.R.S., who kindly put at our disposal the ultra-violet polarimeter.

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378. *The Dependence of Optical Rotatory Power on Chemical Constitution. Part XXXIX.* (−)-2-*Thienylmethylcarbinol.*

By Ian G. Anderson, Michael P. Balfe, and Joseph Kenyon.

Though the linear $1/\alpha$–λ^2 plots of the carbinol (homogeneous and in solution) and of its hydrogen phthalate (in solution) are consistent with simple rotatory dispersion in the visible spectrum, the values for λ_0 of a one-term Drude equation (obtained by extrapolation of $1/\alpha$–λ^2) are not related to the $\lambda_{max.}$ of the observed absorption bands. It is therefore suggested that the dispersion is in fact complex, which is supported by the high values of the dispersion ratios.

The values for λ_0 of the carbinol in different solvents vary over a rather wide range. Its rotatory powers vary in different solvents, but not over an exceptionally wide range, and the rotatory powers of the homogeneous carbinol are relatively insensitive to temperature.

The ultra-violet absorption spectrum of 2-thienylmethylcarbinol [1-(2-thienyl)ethanol] between 2900 and 2200 A. has a maximum at 2335 (ε_{molar} 7840) and an inflexion at 2750 A. (ε_{molar} 14). The main band presumably corresponds to the 2350-A. band of thiophen with $\varepsilon_{max.}$ 4500 in hexane (Braude, *Ann. Reports*, 1945, **42**, 128): substitution in the ring nearly doubles the extinction coefficient without displacing $\lambda_{max.}$. The low-intensity inflection at 2750 A. may be compared (*a*) with the extremely weak band at *ca.* 2700 A. ($\varepsilon_{max.}$ *ca.* 0·16) in thiophen itself, which was recorded by Menczel • (*Z. physikal. Chem.*, 1927, **125**, 161) though not by later workers (cf. Sease and Zechmeister, *J. Amer. Chem. Soc.*, 1947, **69**, 270; Appleby, Sartor, Lee, and Kapranos, *ibid.*, 1948, **70**, 1553; A.P.I. Research Project 44, Ultra-violet Absorption Spectrograms, nos. 38, 136), and with (*b*) similar features in pyrrole and furan (cf. Menczel, *loc. cit.*). All of these may be caused by cyclic conjugation related to the partly aromatic character of the five-membered heterocyclic rings. In 2-thienylmethylcarbinol the nuclear substituent causes a marked increase in intensity of the long-wave band, as is frequently observed with low-intensity " forbidden " transitions.

Table I.

Specific rotatory powers of (−)-2-*thienylmethylcarbinol.*

Solvent and ρ.	Concn., g./100 c.c.	l.	λ, A. 6438.	5893.	5780.	5461.	5086.	4800.	4358.	Ω_D.†
None	—	20°	−19·0°	−23·7°	−24·3°	−28·0°	−33·0°	−37·9°	−49·0°	16·26
None	—	43·5	19·2	—	25·0	28·5	33·5	—	−49·9	—
None	—	64	18·8	—	23·4	26·8	32·0	—	46·3	—
None	—	95	18·1	—	23·0	26·2	31·0	—	43·9	—
Ethyl ether, 1·22	5·01	16	26·0	32·0	32·9	37·5	44·6	50·7	63·3	24·96
Carbon disulphide, 0	5·06	16	28·4	35·2	36·7	41·8	50·3	58·4	76·0	22·65
Ethyl alcohol, 1·74	5·10	20	15·1	17·7	18·7	21·4	24·8	28·3	35·2	13·68
Benzene,‡ 0	2·16	19	—	22·9	24·1	27·3	31·7	36·6	46·1	16·17

‡ −21·6° at 6104, −17·4° at 6708 A. † Rotivity.

Table I gives the rotatory powers of the carbinol in the visible spectrum. The plots of $1/\alpha$–λ^2 for the carbinol, homogeneous at 20°, or in solution (except in carbon disulphide), are linear. However, the dispersion ratios of the homogeneous carbinol (Table II) are not consistent with simple rotatory dispersion, and the dispersion ratios in different solvents vary considerably. Two-term equations, in which λ_1 and λ_2 are respectively greater and less than λ_0, are therefore probably required for an exact expression of the dispersions. The λ_1's may be related to one of the observed absorption bands.

• We are indebted to a Referee for drawing our attention to Menczel's results.

TABLE II.

Dispersion ratios and extrapolated λ_0 values for (−)-2-thienylmethylcarbinol and its hydrogen phthalate.

	Carbinol.								Hydrogen phthalate.	
Solvent:	Homogeneous.				Ethyl ether.	Carbon disulphide.	Ethyl alcohol.	Benzene.	Benzene.	Carbon disulphide.
t:	20°	43·5°	64°	93°.	16°.	16°.	20°.	19°.		
Dispersion ratio	1·74	1·75	1·73	1·68	1·69	1·82	1·65	1·69	1·8	1·8
$[\alpha]_{5893}$										
$[\alpha]_{5461}$										
λ_0 from extrapolated $1/\alpha$–λ_0	2170	2190	2030	1760	1950	2313	1600	1960	2390	2700

TABLE III.

Specific rotatory powers of (−)-2-thienylmethylcarbinol hydrogen phthalate (l, 2; t, 18°).

		$[\alpha]$, A.						
Solvent.	Concn., g./100 c.c.	6438	5893	5780	5461	5086	4800	4358
Benzene	1·87°	−46·6°	−57·9°	−60·5°	−70·0°	−82·3°	−90·0°	−123°
Carbon disulphide	2·10	62·6	79·0	84·7	97·7	116	135	178

The wide variation of λ_0 in different solvents (compare the constancy of λ_0 for phenylcyclohexylcarbinol in different solvents: Part XXXVII) suggests that there are interactions between solvent and carbinol. These may be of dipolar origin, as discussed by Rule (see, *e.g.*, *J.*, 1931, 674), though neither λ_0 values, rotatory powers, nor rotivities lie in the order of the dipole moments of the solvents and the spread of the rotivities is as great as that of the rotatory powers. The rotatory power of 2-thienylmethylcarbinol is much less sensitive than those of glycide phenyl ether (Part XXXVIII) or of 2-(2-hydroxy-*n*-propyl)pyridine (Part XL) to change of solvent, and is not extremely sensitive to temperature changes. It is therefore unnecessary to postulate for 2-thienylmethylcarbinol any form of molecular association such as is suggested for glycide phenyl ether and 2-(2-hydroxy-*n*-propyl)pyridine.

The rotatory dispersions of 2-thienylmethylcarbinyl hydrogen phthalate in benzene and in carbon disulphide (Table III) both give linear plots of $1/\alpha$–λ^2 and dispersion ratios 1·8, the latter indicating that absorption in the near ultra-violet is affecting the rotatory powers. The extrapolated values for λ_0 are in both cases above 2300 A. It is therefore not unlikely that the rotatory dispersion of the phthalate in the visible spectrum is dominated by a Drude term derived from the 2750 A. band of the carbinol, or from the much stronger chromophore in the phthalate radical, at about the same wave-length (Goslawski and Marchlewski, *Bull. Acad. Polon. Sci., A*, 1934, 42). Levene and Rothen (in Gilman's "Organic Chemistry," 1st edn., New York, 1938) have shown that anisotropy in a phenyl chromophore may sometimes make an important contribution to rotatory power.

EXPERIMENTAL.

(±)-2-Thienylmethylcarbinol was obtained by the Grignard reaction from 2-iodothiophen (Minnis, *Org. Synth.*, 1932, **12**, 44) and acetaldehyde in 36% yield calc. on the iodo-compound. Better yields were obtained by reduction of 2-thienyl methyl ketone, which was obtained in 75—80% yield (calc. on thiophen) by the methods described by Johnson and May (*ibid.*, 1938, **18**, 1) and Hartough and Kosak (*J. Amer. Chem. Soc.*, 1946, **68**, 2639): the molar proportions stated in the Experimental section of the latter paper were used. The ketone yielded a semicarbazone, m. p. 189—190°; Steinkopf and Jaffe (*Annalen*, 1917, **413**, 339) record m. p. 190—191°. Meerwein–Ponndorf reduction of the ketone (Kuhn and Dahn, *ibid.*, 1941, **547**, 293; Nazzaro and Bullock, *J. Amer. Chem. Soc.*, 1946, **68**, 2121) gave the carbinol in 70% yield from 20 g. of ketone, the duration of reduction being 1 hour: lower yields were obtained if larger quantities or longer periods of reduction were employed. di-(1-2′-thienylethyl) ether being formed (b. p. 145—147°/14 mm., n_D^{25} 1·5615; cf. Kuhn and Dahn, *loc. cit.*). Though Kuhn and Dahn (*loc. cit.*) report the preparation of the phenylurethane from the carbinol, Campaigne and Dietrich (*J. Amer. Chem. Soc.*, 1948, **70**, 391) were unable to isolate this derivative, and we also have not been able to prepare it. We have obtained the 5-chloromercuri-derivative, m. p. 158—160°, reported by Kuhn and Dahn (*loc. cit.*) to have m. p. 157°.

Hydrogen Phthalate of (±)-2-Thienylmethylcarbinol.—A mixture of the carbinol (53·6 g.), phthalic anhydride (69 g.), and pyridine (50 c.c.) after 5 hours at 70° and 18 hours at 20° was diluted with acetone (250 c.c.) and poured into hydrochloric acid (1 l. of N.) at 0°. The washed precipitate was dissolved in sodium hydrogen carbonate solution and, after extraction of the solution with ethyl ether, the *hydrogen phthalate* was reprecipitated with hydrochloric acid and recrystallised from carbon disulphide; it (42 g.) had m. p. 94° (Found: equiv., 278. $C_{13}H_{12}O_4S$ requires equiv., 276).

The brucine salt which separated from a solution of brucine (204 g.) and (±)-(hydrogen phthalate) (144 g.) in hot ethyl acetate (1 l.) was recrystallised 4 times from ethyl acetate, yielding the brucine salt

(68 g.), m. p. 136°, $[\alpha]^{18}_{5780}$ −50·5, $[\alpha]^{18}_{5461}$ −60·0, $[\alpha]^{18}_{4358}$ −141·5° in chloroform (*c*, 2·45; *l*, 2·0), of the (−)-phthalate. The salt, covered with twice its weight of acetone, was mixed with ice-cold hydrochloric acid. The precipitated (−)-(hydrogen phthalate), recrystallised from carbon disulphide, had m. p. 84°. Rotatory powers are in Table III.

(−)-2-*Thienylmethylcarbinol*.—Potassium hydroxide (4·95 g.) in water (2 c.c.) was added to a solution of the (−)-(hydrogen phthalate) (9·8 g.) in ethyl alcohol (250 c.c.). The mixture was heated for 10 minutes on the steam-bath, cooled, and diluted with water (50 c.c.). Ether (500 c.c.) was added and the mixture washed with brine until neutral. The ethereal solution was dried (Na_2SO_4) and concentrated at 25°. From the residue, (−)-2-thienylmethylcarbinol (3·1 g.), b. p. 88—89°/11 mm., was obtained. Rotatory powers are in Table I. This carbinol yielded a (−)-(hydrogen phthalate) with $[\alpha]^{25}_{5780}$ −56·2° in benzene (*c*, 1·655), *i.e.*, 97% of the rotatory power of the phthalate from which the carbinol was prepared.

Rotivities Ω were calculated from $\Omega = 3[\alpha]/(n^2 + 2)$, by using the weighted means of refractive indices of solvents and solute.

The absorption spectrum was determined by Dr. G. H. Beaven, using a Beckman photo-electric quartz spectrophotometer. Thanks are expressed to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries Limited for grants, and to the Department of Scientific and Industrial Research for a maintenance grant (to I. G. A.).

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379. *The Dependence of Optical Rotatory Power on Chemical Constitution. Part XL. (+)-2-(2-Hydroxy-n-propyl)pyridine.*

By IAN G. ANDERSON, MICHAEL P. BALFE, and JOSEPH KENYON.

The rotatory powers of the carbinol named in the title are not especially sensitive to temperature changes. They vary very widely in different solvents, and are not related to the dipole moment or refractive index of the solvent. In non-hydroxylic solvents, the dispersions are anomalous. In hydroxylic solvents and in the homogeneous carbinol, they are comparatively simple. It is suggested that intermolecular association occurs in the homogeneous carbinol, that self-association of the carbinol is lessened in hydroxylic solvents, and that intramolecular association occurs in non-hydroxylic solvents; also that intramolecular association increases the contribution of the pyridine chromophore to the rotatory power, this stimulation of the longer wave-length term in the dispersion equation making the dispersion anomalous.

TABLE I summarises the absorption spectrum of 2-(2-hydroxy-n-propyl)pyridine (in ethyl-alcoholic solution) between 3000 and 2200 A. It shows a region of absorption, with $\lambda_{max.}$ at 2620 A. accompanied by some fine structure; ε falls to a minimum at 2260 A. ($\varepsilon_{min.} = 640$) and then rises as λ decreases below 2250 A., indicating the presence of a stronger band with $\lambda_{max.}$ below 2200 A. These two bands are related to the bands at 2500 and 1950 A. in the spectrum of pyridine (Braude, *Ann. Reports*, 1945, **42**, 128), shifted to longer wave-lengths by nuclear substitution.

Table II gives the rotatory powers of the (+)-carbinol. The rotatory power of the homogeneous carbinol is not especially sensitive to temperature changes. The rotatory powers at 20° give a linear $1/\alpha$–λ^2 plot, and the extrapolated λ_0 is 2500, which is not far removed from the long-wave absorption band and suggests that the pyridine chromophore may be optically active.

The rotatory powers in solution do not show any simple relation to the dipole moments of the solvents; they vary over a wider range than can be explained by variations in refractive index, as is shown by the values for rotivity (Ω in Table II). In each of the solvents chloroform, carbon tetrachloride, ethyl acetate, ethyl ether, acetone, dioxan, and benzene (2% solution), one or more of the characteristics of anomalous dispersion (inflexion, maximum, or reversal of sign in the α–λ plot) are apparent. In these cases a Drude equation with two terms of opposite sign would be required to fit the dispersion; in transparent regions, the term of shorter wave-length in such an equation dominates the rotatory power and must therefore be (+) in the present example. In nitromethane, curvature of the $1/\alpha$–λ^2 plot indicates complex dispersion. In carbon disulphide, water, ethyl alcohol, and acetic acid, $1/\alpha$–λ^2 plots are linear; in the first, $\lambda_0 = 0$, showing that a one-term equation is not valid. In the three hydroxylic solvents, the dispersion ratios are fairly constant and their high values may be ascribed to rotatory contributions arising from bands in the far ultra-violet, since the values of λ_0 are not sufficiently near the observed absorption band at 2620 A. Though the rotatory dispersion therefore cannot be simple, it does not show the marked anomalies observed in the non-hydroxylic solvents and, since the signs of rotatory power are the same in both kinds of solvents, the contribution of the term of longer wave-length must be lessened in the hydroxylic solvents.

TABLE I.

Ultra-violet absorption spectrum of 2-(2-*hydroxy*-n-*propyl*)*pyridine* (*in ethyl alcohol*).

$\lambda_{max.}$	2500 •	2570	2620	2685
$\epsilon_{max.}$	2400	3190	3620	2990

• Inflexion.

TABLE II.

Specific rotatory powers of (+)-2-(2-*hydroxy*-n-*propyl*)*pyridine*.

Solvent and μ.		t.	λ, A. 6708.	6438.	6104.	5893.	5780.	5461.	5086.	4800.	4358.	$[\alpha]_{6438}/[\alpha]_{5461}$	λ_0	Ω 5893.
None	*d*, 1·049	20°	—	46·3°	—	55·5°	59·6°	68·6°	82·3°	95·4°	124°	1·81	2500	38·7
	d, 1·045	25	—	43·9	—	—	57·2	65·9	77·4	—	118	1·79	—	—
	d, 1·030	43	—	40·1	—	—	50·1	57·6	68·2	—	—	—	—	—
	d, 1·016	59	—	35·9	—	—	45·1	51·9	61·7	—	—	—	—	—
	d, 0·983	98	—	—	—	—	36·5	41·7	—	—	—	—	—	—
Ethyl ether, 1·22	*c*, 2·103	18	—	9·5	—	10·2	—	11·7 •	12·1	—	6·7	0·57	—	7·98
Benzene, 0	*c*, 1·887	21·5	22·0°	22·0	23·6°	26·1	27·3	29·7	31·1	31·6	31·6	1·06	—	18·42
	c, 20·06	18	26·2	29·4	31·7	34·4	35·4	39·4	45·1	50·3	58·5	1·48	—	24·24
Carbon tetrachloride, 0	*c* 2·135	19·5	13·6	14·1	15·5	16·6	16·9	17·6	17·1	16·0	9·8	0·56	—	12·03
Chloroform, 1·18	*c*, 2·392	21	—	1·9	—	5·8 •	6·1	—	4·6	—	−9·2	—	—	4·26
Ethyl acetate, 1·81	*c*, 2·103	17·5	—	—	—	—	10·4	11·0 •	11·6	—	8·3	0·75	—	—
Acetone, 2·74	*c*, 2·011	21	9·5	10·2	—	11·5	12·0	13·7	14·7	—	12·0	0·88	—	8·97
Carbon disulphide, 0	*c*, 2·122	16	—	51·8	—	61·0	65·0	71·6	83·7	95·1	114	1·60	0	39·3
Water, 1·9	*c*, 2·236	21·5	—	50·3	—	61·5	64·4	74·3	87·7	102	135	1·81	2365	48·6
Ethyl alcohol, 1·74	*c*, 2·074	16·5	29·2	33·5	36·6	39·5 •	41·4	48·2	57·4	66·2	86·1	1·79	2360	30·6
Acetic acid, 1·04	*c*, 2·139	17	—	75·2	—	90·0 •	94·0	109	131	154	195	1·79	2160	69·3
Nitromethane, 3·13	*c*, 2·169	20	—	28·1	—	33·0 •	33·9	37·8	44·9	49·3	58·7	1·55	—	25·29
Dioxan, 0	*c*, 2·167	18	23·0	23·7	25·8	27·7	29·3	32·7	38·4	43·3	49·8	1·52	—	20·64
	c, 2·119	25	—	27·4	—	—	28·3	33·1	38·2	—	50·0	1·51	—	—
	—	63	—	18·9	—	—	21·2	25·5	34·0	—	42·0	1·65	—	—

• Interpolated.

The effects of solvents on the rotatory power may be explained by the following assumptions :

(i) In the homogeneous carbinol, the association is intermolecular and the dispersion term associated with the 2620-A. band is significant.

(ii) When the carbinol is diluted with non-hydroxylic solvents, its molecules, being more separated from one another, associate intramolecularly. The contribution to the rotatory power from the pyridine chromophore, which is the longer wave-length term in the rotatory power expression, is thereby stimulated, and the rotatory dispersion becomes complex. Such an association (hydrogen bonding) between the hydroxyl group and the nitrogen atom, is stereochemically possible and would introduce the possibility of molecular dissymmetry as well as affecting the pyridine chromophore. The two observations on benzene solutions show that at high concentration (*c*, 20) the dispersion is less complex ($1/\alpha$–λ^2 is linear though the dispersion ratio is 1·48, and λ_0 is imaginary), than in more dilute solution (*c*, 2·0), where the dispersion becomes anomalous : continued reduction of the molecular association by dilution would explain this.

(iii) In hydroxylic solvents, intra- and inter-molecular associations are prevented by association with the solvent : the rotatory power is dominated by a short-wave length (far ultra-violet) term and is comparatively simple.

Esterification of the alcohol would prevent such forms of association. Results with the (+)-acetate (Table III) are consistent with this suggestion. It is pseudo-simple, whether the acetate is homogeneous or in solution in two non-hydroxylic solvents. In all three cases

$1/\alpha-\lambda^2$ plots are linear, extrapolated values of λ_0 are about 2250 A., and dispersion ratios are 1·75. The *p*-diphenylylurethane is probably too complex a molecule to give a satisfactory test of the suggestion (it contains an additional ultra-violet chromophore), but in two non-hydroxylic and one hydroxylic solvent it gives linear $1/\alpha-\lambda^2$ plots and dispersion ratios of about 1·6, though the λ_0's vary very widely.

TABLE III.

Specific rotatory powers of esters of (+)-2-(2-*hydroxy*-n-*propyl*)*pyridine*.

Solvent.		*t*.	λ, A. 5893.	5780.	5461.	5086.	4800.	4358.	Dispersion ratio.	λ_0.
Hydrogen phthalate.										
5N-HCl	*c*, 2·049	19·5°	58·5°	79·0°	92·2°	112°	132°	178°	1·93	2730
Water	*c*, 0·945	20	—	76·8	88·5	—	—	167	1·89	2600
N-NaOH	*c*, 1·957	20	—	—	96·0	—	—	—	—	—
Acetate.										
None	*d*, 1·048	23	8·4	10·8	12·3	14·4	16·4	21·4	1·74	2120
Benzene	*c*, 2·161	23	12·5	15·5	18·3	21·6	—	32·2	1·76	2280
Carbon tetrachloride	*c*, 1·992	23	9·3	11·3	13·3	15·1	—	23·3	1·75	2390
Diphenylylurethane.										
Benzene ...	*c*, 2·015	20	10·0	11·2°	—	13·7	15·9	—	22·0	1·60	0
Ethyl alcohol	*c*, 2·215	17·5	25·7	31·6	32·7	36·8	43·3	—	60·3	1·63	1565
Carbon tetrachloride	*c*, 1·337	19	7·9	8·6	10·1	11·6	12·4	—	18·4	1·59	1380

The hydrogen phthalate cannot be used to test the suggestion because it is soluble only in aqueous solutions (it probably exists in the zwitterion form); its dispersion ratios are high, probably on account of increased absorption in the ultra-violet, and it gives linear $1/\alpha-\lambda^2$ plots. The rotatory powers $[\alpha]_{5461}$ of the hydrogen phthalate are 88°, 92°, and 96° respectively in water (in which it probably contains positively and negatively charged groups), in hydrochloric acid (in which it contains a positively charged group only), and in sodium hydroxide (in which it contains a negatively charged group only); this comparative insensitivity to the polarity of the substituents is somewhat unusual.

The rotatory power of tetrahydrofurfuryl alcohol resembles that of 2-(2-hydroxy-n-propyl)-pyridine in that it is very sensitive to change in solvent, but not especially so to change of temperature. In Part XXXV (*J.*, 1941, 312) it was argued that the comparative insensitivity to temperature shows that labile structures do not occur in the alcohol. However, since the rotatory powers of tetrahydrofurfuryl alcohol in solution are not related to the dipole moments of the solvents, and the rotivities (calculated from data given in Part XXXV) vary as widely as the rotatory powers, the arguments now developed suggest that alterations in the molecular species do occur on change of solvent, as was suggested by Irwin, Thesis, London, 1947). Intramolecular association (hydrogen bonding) between the two oxygen atoms is stereochemically possible in tetrahydrofurfuryl alcohol.

EXPERIMENTAL.

(±)-2-(2-*Hydroxy*-n-*propyl*)*pyridine*.—This was prepared as described by Walter, Hunt, and Fosbinder (*J. Amer. Chem. Soc.*, 1941, **63**, 2771; *Org. Synth.*, 1943, **23**, 83) from the lithium derivative of α-picoline and acetaldehyde; the purified carbinol was obtained in 45% yield. It did not yield crystalline salts with optically active acids.

(±)-*Hydrogen Phthalate*.—From a solution of the carbinol (51 g.) and phthalic anhydride (55 g.) in acetone (140 c.c.), warmed under reflux for 30 minutes, the hydrogen phthalate (91 g.; m. p. 138—141°) separated during 18 hours. It is insoluble in carbon disulphide, cyclohexane, benzene, acetone, and ethyl acetate, sparingly soluble in chloroform or cold water, dissolves readily in hot water (from which it does not separate on cooling), ethyl alcohol, aqueous acids, or alkalis. These solubilities suggest that it exists as the zwitterion, and is only slowly soluble in cold water because it is not easily wetted.

(+)-2-(2-*Hydroxy*-n-*propyl*)*pyridine*.—Brucine (197 g.) and the (±)-(hydrogen phthalate) (142 g.) were dissolved in hot acetone (1250 c.c.); the crystalline brucine salt (m. p. 148—150°) which separated during 18 hours at room temperature was recrystallised from ethyl acetate (3950 c.c.), yielding 100 g. of brucine salt, m. p. 154—156°, with $[\alpha]_D^{20}$ −20·2° in chloroform (*c*, 2·147), which was not altered by further recrystallisation. A mixture of the salt (10 g.) and 5N-sodium hydroxide (10 c.c.) was heated on the steam-bath for 30 minutes, cooled, and extracted with ether. The ethereal solution was dried (K_2CO_3) and concentrated, and the residue distilled, yielding the (+)-carbinol (1·5 g.), b. p. 111°/10 mm., n_D^{20} 1·5142. Rotatory powers are in Table II. The usual procedure for conversion of alkaloid salt to carbinol *via* the hydrogen phthalate is not applicable in this case, because the phthalate is soluble in aqueous solutions

and not in organic solvents. The filtrate from the first crystallisation yielded a *lævo*carbinol, $[\alpha]_D^{\infty} -42{\cdot}0°$ in carbon disulphide (*c*, 2·2); this was converted into the hydrogen phthalate, from which a crystalline alkaloidal salt could not be obtained. Rotivities, Ω in Table II are calculated as $3[\alpha]_{5893}/(n^2 + 2)$, by using the weighted means of refractive indices of solvents and solute.

The (+)-(hydrogen phthalate) was prepared from the (+)-carbinol as described above. Rotatory powers are in Table II. The rotatory power in sodium hydroxide solution is an extrapolation to zero time from the following observations of $[\alpha]_{5461}$/mins. after dissolution: 79°/24, 70°/45, 61°/65, 53°/90, 36°/240, 33°/2670. The final observation is a little lower than would be derived from the equivalent concentration of (+)-carbinol in water, *viz.*, +37°.

(+)-2-(2-Hydroxy-*n*-propyl)pyridine acetate was prepared from equal volumes of the carbinol (2·2 g.) and acetic anhydride, heated at 60° for 3 hours, diluted with ether, washed with N-sodium hydroxide till neutral, dried (Na_2SO_4), and concentrated. The (+)-acetate (1·3 g.), obtained from the residual oil, had b. p. 124—125°/19 mm. n_D^{25} 1·4915, d_4^{25} 1·048. Rotatory powers are in Table III.

(+)-2-(2-*Hydroxy*-n-*propyl*)*pyridine* p-*diphenylylurethane*. A solution of the (+)-carbinol (0·5 g.) and *p*-diphenylylcarbimide (0·75 g.) in benzene (10 c.c.) was heated under reflux for 30 minutes. On cooling, the (+)-urethane crystallised and, recrystallised from benzene–light petroleum, had m. p. 134° (0·85 g.). Rotatory powers are in Table III.

The absorption spectrum was determined by Dr. G. H. Beaven, using a Beckman photoelectric quartz spectrophotometer. Thanks are expressed to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries Limited for grants, and to the Department of Scientific and Industrial Research for a maintenance grant (to I. G. A.).

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380. *The Dependence of Optical Rotatory Power on Chemical Constitution. Part XLI.*

By M. P. BALFE.

The use of rotation and dispersion data in the discussion of labile molecular configurations, as applied in the preceding communications, is briefly surveyed.

SINCE 1928, optically active alcohols have been prepared in this laboratory for use in the study of reaction mechanisms, rather than for the study of optical activity itself. In 1942 the derivation of a two-term Drude equation to fit the rotatory dispersion of 2-furylmethylcarbinol (Airs, Balfe, Irwin, and Kenyon, *J.*, 1942, 531) encouraged us to consider the rotatory dispersion of *cyclo*hexylphenylcarbinol, which was in preparation at that time, and to prepare three other optically active compounds with heterocyclic substituents, *viz.*, 2-thienylmethylcarbinol, 2-(2-hydroxy-*n*-propyl)pyridine, and glycide phenyl ether, for similar examination. In the preceding communications it is suggested, mainly on the basis of changes in rotatory dispersions, that molecular association occurs in the last two substances. The purpose of the present communication is to examine the basis for such suggestions: most of the matters involved are discussed fully by Lowry ("Optical Rotatory Power," London, 1935), Kuhn (*Trans. Faraday Soc.*, 1930, **26**, 293), Levene and Rothen (in Gilman's "Organic Chemistry," 1st Edn., New York, 1938), and Kauzmann, Walter, and Eyring (*Chem. Reviews*, 1940, **26**, 339).

A comparison of the magnitudes of the rotatory powers of different substances, under the same experimental conditions, can be related to differences in structure, notably in the observation that ring structures produce a much higher rotatory power than do isomeric open-chain structures (see, *e.g.*, the values recorded by Kauzmann, Walter, and Eyring, *loc. cit.*). For the present purpose, however, we are concerned with changes in structure on variation of the experimental conditions. These variations may alter the rotatory power, even if the structure of the optically active molecules remains substantially unchanged, and such effects must be eliminated if, as described later, it is desired to relate changes in optical rotation to changes in structure. We also suggest that changes in rotatory dispersion may be used as an indication of changes in structure, because rotatory dispersion is controlled by the optically active (or anisotropic) bands in the absorption spectrum, the frequencies of which are not, so far as is known, greatly altered by changes of, *e.g.*, temperature or solvent. If then such a change in conditions of observation causes a change in dispersion, it would appear that the dispersion becomes controlled by new absorpton frequencies, which must imply some change in the molecule.

It is assumed (following Lowry, and Levene and Rothen, *opp. cit.*) that, in regions of transparency, rotatory dispersion can be expressed by a Drude equation $\alpha_\lambda = \Sigma \frac{A_1}{\lambda^2 - \lambda_1^2}$, the

constants λ_1, λ_2 . . . being frequencies of anisotropic absorption bands. "Simple" dispersion is expressed by a one-term equation and "complex" dispersion by a two-term equation (if the terms have opposite signs and $k_1 < k_2$, $\lambda_1 > \lambda_2$, the dispersion is "anomalous"); it is rarely that more than two terms are required to fit the dispersion in accessible wave-lengths. The most secure basis for comparison of rotatory dispersions is given by calculation of Drude equations from selected observations, to fit the dispersion curves observed under the different experimental conditions. It is, however, essential that the observations should be carried as far as possible into the ultra-violet, and unfortunately the facilities for so doing are not commonly available. Moreover, it is not always possible to derive a Drude equation to fit observations which extend into the ultra-violet. One possible reason for this is that the measurements may not be sufficiently delicate (the calculations can be very sensitive to small variations in rotatory powers).

Even when it is not possible to derive an equation from the observations of rotatory power alone, it is usually possible to calculate one or more which fit tolerably well the observations, by assuming values for the characteristic frequencies λ_1, λ_2, and adjusting the k constants by trial and error. The procedure is less elegant than direct calculation, but would appear to be applicable for the present purpose. Some reasonable basis is of course necessary for the assumed frequencies: for example, characteristic frequencies of optically active substances of similar structure, or absorption frequencies in the spectrum of the substance under examination. It may be found that several equations can be so derived to fit approximately the dispersion, but, if a change in experimental conditions causes changes in the constants of all of such several equations, then it would appear that the change in conditions has caused a change in the optically active molecules. Indications of changes in dispersion may also be obtained by the classification into simple dispersion (linear plot of $1/\alpha$ against λ^2) and complex dispersion (curvature of plot): extrapolation of linear plots to the $1/\alpha$ axis gives the value of λ_0 of the one-term equation. In most cases this is composite, and of no exact physical significance, but notable changes in it must reflect changes in the constants of the dispersion equation, as shown by Hunter (*J.*, 1924, **125**, 1198) and Levene and Rothen (*op. cit.*). Similar comments apply to the use of the dispersion ratio, $\alpha_{4358}/\alpha_{5461}$ (Lowry, *op. cit.*, p. 132), which, if a one-term equation is applicable, is 1·61 for λ 1000 A., 1·65 for λ 1500 A., 1·73 for λ 2000 A., and 2·09 for λ 3000 A. Dispersion ratios below 1·57 indicate that the dispersion equation has two terms of opposite sign; ratios between 1·61 and 1·65 indicate that a one-term equation applies (particularly if the ratio does not change with solvents); ratios above 1·70, if constant in different solvents, indicate absorption in the near ultra-violet; if varying with solvent, they indicate that a two-term equation is required (Lowry, *op. cit.*).

The variables which we have used are temperature and solvent. Both may alter the optical rotation because they alter the refractive index of the medium. This effect can be eliminated, perhaps not completely (compare the results of Kenyon and Platt, *J.*, 1939, 633, with an optically active hydrocarbon), but probably sufficiently for the present purpose, by use of an expression such as Beckmann and Cohen's "rotivity" $\Omega\{= 3[\alpha]/(n^2 - 2)\}$ (*J. Chem. Physics*, 1936, **4**, 784; 1938, **6**, 183); this expression can be derived from quantum-mechanical concepts of the theory of optical rotatory power (Kauzmann *et al.*, *loc. cit.*). The temperature coefficient of density, which affects the number of molecules influencing the beam of polarised light, is eliminated in the calculation of specific rotatory power. Increase in temperature also reduces specific rotatory power because it gives increased freedom of rotation about single bonds (this decrease is not observed in the rotatory powers of substances which have a cyclic, and therefore rigid, structure). The total decrease in specific rotatory power caused by the temperature coefficients of refractive index and freedom of rotation is not more than 10—20% on 100° rise in temperature. If then a specific rotatory power is very greatly altered by change in temperature, it would seem reasonable to assume that there has been some alteration in molecular configuration, or in an equilibrium condition thereof, which is equivalent to an alteration in the optically active species.

When the rotatory powers (see, *e.g.*, Rule, Smith, and Harrower, *J.*, 1933, 386) or preferably the rotivities (Kauzmann, Walter, and Eyring, *loc. cit.*) of a given solute in a variety of solvents are plotted against the dielectric constants (or a function thereof), a fairly clear relation can sometimes be observed. This is ascribed to solvent–solute interactions, which are outside the scope of the present investigations. We therefore ascribe to changes in the solute, only those changes in rotatory powers in different solvents, which are not caused by changes in refractive index and do not show any relation to the dielectric constants of the solutions.

Kauzmann, Walter, and Eyring (*loc. cit.*) observed that the sensitivity of rotatory power to

influences such as temperature, solvent, and small changes in structure make it a potentially powerful tool for investigating minor alterations which other molecular properties (*e.g.*, refractivity) are incapable of disclosing; Rule (*J.*, 1933, 1217, and earlier papers, summarised by Lowry, *op. cit.*) had made a similar comment (the comparison is with other methods in which no chemical disturbance of structure occurs). The comment seems valid in principle. In its practical application, however, as outlined in the present communications, there remains a need for increased certainty of interpretation, which may come with further applications on similar lines. Bernstein and Pedersen (*J. Chem. Physics*, 1949, **17**, 885) have recently reported a somewhat similar application of rotivity data to discussion of the configurations of *sec.*-butyl alcohol; extension of the present investigations is not contemplated.

If the procedures here outlined do, in fact, lack precision, this is not due to fundamental deficiencies in the theoretical study of rotatory power, regarding which Kauzmann, Walter, and Eyring (*loc. cit.*) observe that " the problem of optical rotation can be said to be solved in principle." Nor does it seem that increased accuracy in observations of rotatory power in the visible or near ultra-violet regions would improve the discussions. So far as discussions based on dispersion data are concerned, the most useful advance would be an extension of the range of wave-lengths in which rotations can be measured. Even the range covered by visible and accessible ultra-violet frequencies is only a small part of the spectral region in which optical activity may be manifested (see Kuhn, *loc. cit.*). Comparisons of complete optical rotatory spectra would clearly be preferable to comparisons of calculated characteristics of inaccessible regions based on observations in the comparatively narrow accessible regions. There seems, however, to be no immediate prospect of extending optical rotatory spectra into the vacuum-ultra-violet; quantitative absorption spectra have not yet been extended into this region, though qualitative and some semi-quantitative observations have been made (see Platt and Klevens, *Rev. Mod. Physics*, 1944, **16**, 182). Such an extension of rotatory spectra would be of intrinsic interest, but whether it would be more rewarding, in the study of labile configurations, than the study of infra-red absorption, in which advances have already been made, is open to question.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, March 16th*, 1950.]

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381. *The Chemistry of Hop Constituents. Part I. Humulinone, a New Constituent of Hops.*

By A. H. COOK and G. HARRIS.

Extraction of the cones of *Humulus lupulus* (the common English hop) led to the isolation of *humulinone*, a new constituent of the petroleum-soluble hop resins.

IN general, extraction of the cones or lupulin glands of a number of varieties of hops with organic solvents has in the past yielded two well-known crystalline compounds, humulone, $C_{21}H_{30}O_5$, and lupulone, $C_{26}H_{34}O_4$, to which structures were assigned by Wieland *et al.* after preliminary work on their constitution by Wöllmer (*Ber.*, 1916, **49**, 780; 1925, **58**, 672; cf. Barth and Lintner, *Ber.*, 1898, **31**, 2022; Bungener, *Bull. Soc. chim.*, 1886, **45**, 487; Hayduck, *Wochenschr. Brau.*, 1888, 937; Lintner and Schnell, *Z. ges. Brauwesen*, 1904, **27**, 666; Wieland, Schneider, Martz, and Hoek, *Ber.*, 1925, **58**, 102, 1012; 1926, **59**, 2352). During the working up of methanolic extracts of the cones of the Worcester Fuggle or Kent Golding varieties of hops, incidental to a wider examination of hop constituents, a new compound was obtained. This compound, termed *humulinone*, was isolated as the crystalline *sodium* salt, $C_{21}H_{29}O_5Na$, by treatment of the petroleum-soluble material with sodium hydrogen carbonate and was present to the extent of 1·0—2·0% by weight of the cones. Under the conditions used and in the presence or absence of air, both humulone and lupulone were shown to be stable, as was *iso*humulone which has been regarded as an isomer of humulone and is obtained from humulone by short treatment with hot alkali (Windisch, Kolbach, and Schleicher, *Wochenschr. Brau.*, 1927, **44**, 453, 473, 485, 497; Verzele and Govaert, *Congr. Intern. Inds. Fermentation, Confs. et Communs.*, 1947, 297). Little doubt remained, therefore, that humulinone was present in the hop cones as such and was not formed from other compounds.

The new compound was isolated directly from a light-petroleum solution of the hop constituents by treatment with aqueous sodium hydrogen carbonate or, more economically, together with humulone as a mixture of lead salts from 90—95% methanol. In this way,

lupulone was obtained from the filtrate resulting on removal of the lead salt, by direct crystallisation of the residue from light petroleum. Humulinone was obtained from the lead salts by regeneration with sulphuric acid and treatment with sodium hydrogen carbonate. Acidification of the sodium salt gave free humulinone, $C_{21}H_{30}O_5$, a white crystalline substance which did not crystallise from solvents. This and its sodium salt appeared from their ultra-violet absorption spectra to possess tautomeric structures; the significant data together with the absorption characteristics of humulone, lupulone, and *iso*humulone (all in ethanol) are given in Table I.

TABLE I.

	$\lambda_{max.}$ A.	$E^{1\%}_{1\,cm.}$		$\lambda_{max.}$ A.	$E^{1\%}_{1\,cm.}$
Humulinone	2290	330	Lupulone	2280	340
	2680	250		2800	150
	2800	300		3380	250
Sodium salt of humulinone	2500	470	*iso*Humulone	2230 } 2280 }	350
	2590	500			
	2670	470		2680	280
Humulone	2370	380		2800	250
	2820	230			
	3300	220			
	3400 •	180			

• Inflexion.

The absorption curves of humulinone and *iso*humulone were almost superposable, and both substances gave a purple colour with alkaline sodium nitroprusside. Humulinone resembled humulone and *iso*humulone on potentiometric titration with alkali, behaving as a monobasic acid, and back-titration with acid indicated that it had not suffered any change. It was a strong acid of pK_a 2·7, as compared with pK_a values of 5·5 and 3·4 for humulone and *iso*humulone respectively. At $2{\cdot}1 \times 10^{-4}$ mm. pressure, humulinone distilled with decomposition at 125°. It contained two double bonds (iodine value), five active hydrogen atoms (Zerewitinoff), and one *gem*-dimethyl group (Kuhn–Roth oxidation).

Hydrolysis of humulinone with hot aqueous sodium hydroxide yielded acetone and *iso*hex-3-enoic acid,• together with a mixture of unidentified acidic products. It thus seemed that this acid might be that isolated on alkaline hydrolysis of humulone, and not the 2-enoic acid as generally supposed. This proved to be the case. The other products isolated from humulone in this reaction were *iso*butyraldehyde, humulinic acid (cf. Wöllmer and Wieland *et al.*, *locc. cit.*), and acetone, of which the last had not previously been obtained. The structure of humulinone, as of humulone and lupulone, is being investigated.

TABLE II.

Activities (Dilutions, w/v).

	M. phlei.	*B. coli.*	*Staph. aureus.*	*Lactobacillus β.*†	*Lactobacillus plantarum.*
Lupulone	1 : 100,000	Inactive	1 : 400,000	Inactive	1 : 40,000
Humulone	1 : 10,000	,,	1 : 50,000	1 : 20,000	1 : 100,000
*iso*Humulone	1 : 10,000	,,	Inactive	1 : 20,000	1 : 200,000
Humulinone	1 : 10,000	,,	,,	1 : 10,000	1 : 20,000

† The strains of lactobacilli, kindly supplied by Dr. T. K. Walker, are common sources of infection in beers.

In view of the recent interest in lupulone as a tuberculostatic agent *in vivo* in mice (Yin-Ch'ang Chin, Anderson, Alderton, and Lewis, *Proc. Soc. Exp. Med.*, 1949, **70**, 158; Chin and Anderson, *Fed. Proc.*, 1949, **8**, 281), humulinone was compared with lupulone, humulone, and *iso*humulone as inhibitors of *Mycobacterium phlei* and other organisms (Table II) (cf. Blakebrough, M.Sc. Thesis, Manchester, 1948). It may be seen that humulinone was not comparable with lupulone in activity against *M. phlei*.

EXPERIMENTAL.

Isolation of Humulinone.—(*a*) The cones of Worcester Fuggle hops (500 g.) were kept in methanol (5 l.) under nitrogen for 20 hours. Filtration and evaporation of the methanolic extract in a vacuum gave a green oil (95 g.), which was extracted with warm light petroleum (b. p. 40—60°; 700, 250 c.c.). Evaporation of the light petroleum extracts gave an oil (*A*) (28 g.). A part (15 g.) was dissolved in methanol (220 c.c.) and water (11 c.c.), and the total lead salt precipitated with 90% methanolic lead

• Geneva nomenclature.

acetate using aqueous sodium sulphide as external indicator. After 20 hours the salt (8·75 g.) was collected, finely ground, and suspended in methanol (85 c.c.), and 30% sulphuric acid (12 c.c.) was added to the ice-cold suspension. The mixture was well shaken, lead sulphate removed, and the filtrate diluted with water (250 c.c.) and light petroleum (90 c.c.). After re-extraction of the aqueous layer, the light petroleum extracts were washed and dried. Evaporation gave an oil (5·55 g.), which was set aside with saturated aqueous sodium hydrogen carbonate (30 c.c.) and ether (30 c.c.) for 2—3 days. The *sodium* salt of humulinone separated, and concentration of the ethereal filtrate and addition of light petroleum (25 c.c.) gave a second crop (total yield, 1·15 g.). Recrystallised from methanol–ether, it separated as colourless wedge-shaped prisms, m. p. 227° (decomp.) (Found : C, 63·4, 62·5, 62·7 ; H, 7·5, 7·2, 7·5 ; Na, 5·8, 5·75, 6·05 ; OMe, 0. $C_{21}H_{29}O_4Na$ requires C, 63·0 ; H, 7·3 ; Na, 5·75 ; OMe, 0%). With ethanolic ferric chloride, it gave an orange colour.

(*b*) The oil (*A*) (0·5 g.) was set aside with ether (10 c.c.) and saturated aqueous sodium hydrogen carbonate (10 c.c.) for 7 days. The ether was separated, rapidly dried, and allowed to evaporate after the addition of a little light petroleum. Yield : 0·114 g. of material, m. p. 224° (decomp.).

(*c*) The cones of Kent Golding hops (250 g.) were kept as above with methanol (3 l.) for 25 hours. Evaporation, extraction of the residue with warm light petroleum (150, 100, 50 c.c.), and evaporation of the petroleum solution gave an oil (26·5 g.). This oil was treated with ether (250 c.c.) and saturated aqueous sodium hydrogen carbonate (250 c.c.). After a few days, the product (0·95 g.) was filtered off. Drying and addition of light petroleum (200 c.c.) to the ethereal filtrate brought the total yield to 3·25 g. (1·7% of the wt. of cones).

Humulinone.—The sodium salt (0·109 g.) was shaken with ether (20 c.c.) and 2*N*-hydrochloric acid until the solid had completely disappeared. Washing, drying, and evaporation of the ether gave *humulinone* as a white solid (0·103 g.), m. p. 74° (Found : C, 66·8, 66·8 ; H, 8·0, 8·1 ; active H, 1·33, 1·43 ; Kuhn–Roth oxidation gave 1·05, 1·09 mol. of acetic acid ; I value, 73·6, 76·8% ; equiv., 367. $C_{21}H_{30}O_4$ requires C, 66·65 ; H, 8·0 ; active H for 5H, 1·33 ; I value for 2 double bonds, 67·1% ; equiv., 378·5). With bromine in carbon tetrachloride, hydrogen bromide was evolved. Humulinone was soluble in all organic solvents, but insoluble in water.

Stability of Humulone to Sodium Hydrogen Carbonate.—Humulone (0·85 g.) was kept in ether (10 c.c.) and saturated aqueous sodium hydrogen carbonate (15 c.c.) for 6 days under nitrogen. A similar experiment was conducted with the omission of nitrogen. In each case, separation, washing, and drying the ethereal layer gave a yellow, hygroscopic solid, insoluble in light petroleum, which presumably was the sodium salt of humulone since treatment with methanolic lead acetate gave the lead salt (1·2 g.). Decomposition of the salt as above gave humulone, m. p. 60—65° (0·6 g.), identified as the *o*-phenylenediamine complex (0·65 g.), m. p. 111°, undepressed on admixture with authentic material (m. p. 117°).

Similar treatment of lupulone or *iso*humulone gave unchanged starting materials ; the former had m. p. 93°, after crystallisation from light petroleum (b. p. 40—60°) ; *iso*humulone had b. p. 100°/2 × 10^{-4} mm. (Found : C, 69·4 ; H, 8·6. Calc. for $C_{21}H_{30}O_5$: C, 69·6 ; H, 8·3%). With ethanolic ferric chloride, *iso*humulone gave a carmine-red colour and with alkaline sodium nitroprusside a strong red colour.

Hydrolysis of Humulinone.—The sodium salt of humulinone (0·400 g.) was added to 0·1*N*-sodium hydroxide (50 c.c.), which had been refluxed for 1·5 hours in a current of nitrogen. The solution was distilled slowly in a current of nitrogen, the volume being made up as necessary with boiled-out water. The distillate was collected under 6*N*-hydrochloric acid containing 2 : 4-dinitrophenylhydrazine (*A*). After 40 minutes the solution was acidified with 2*N*-sulphuric acid, and the acid solution distilled (40 c.c.). The distillate was extracted with chloroform (4 × 20 c.c.) (*B*). Solution *A* was extracted with benzene (4 × 20 c.c.), and the washed, dried benzene extract evaporated. The residue in benzene (3 c.c.) was placed on a column of alumina (Spence, Type H, 21·5 × 1·2 cm.) and the broad yellow band eluted with benzene. Evaporation of the eluate yielded orange needles (98 mg.), m. p. 126°, undepressed on admixture with authentic acetone 2 : 4-dinitrophenylhydrazone, after recrystallisation from methanol (5 c.c.) (Found : N, 23·1. Calc. for $C_9H_{10}O_4N_4$: N, 23·5%). Solution *B* was evaporated to give an oil (121 mg.) and neutralised with 0·59 c.c. of 0·987*N*-potassium hydroxide in water (0·5 c.c.). After addition of 2*N*-hydrochloric acid (0·05 c.c.) and *p*-bromophenacyl bromide (120 mg.) in ethanol (2·5 c.c.), the mixture was heated under reflux for 1 hour. On cooling the crystalline product had m. p. 97—98°, and, recrystallised from aqueous ethanol, *p-bromophenacyl* iso*hex-3-enoate* separated as rectangular plates, m. p. 97—98° (Found : C, 53·9, 54·1 ; H, 4·9, 4·9 ; Br, 25·65, 25·2. $C_{14}H_{15}O_3Br$ requires C, 54·0 ; H, 4·9 ; Br, 25·7%).

iso*Hex-2-enoic Acid.*—This was prepared by the method of Goldberg and Linstead (*J.*, 1928, 2353) and had b. p. 116—117°/19 mm. The *p*-bromophenacyl ester was prepared as above and separated as colourless prisms, m. p. 74—75°, from benzene–light petroleum (lit., m. p. 71—72°) (Found : C, 54·0 ; H, 4·9 ; Br, 25·5%). The m. p. was depressed on admixture with the derivative above.

iso*Hex-3-enoic Acid.*—Prepared by the method of Goldberg and Linstead (*loc. cit.*), this had b. p. 107—108°/13·5 mm. The *p*-bromophenacyl ester, prepared as above and recrystallised from aqueous ethanol, had m. p. 97—98°, undepressed on admixture with the above derivative (Found : C, 54·0 ; H, 4·9 ; Br, 25·6%).

Hydrolysis of Humulone.—Humulone (1·0 g.) was treated by the above method with 0·1*N*-sodium hydroxide (100 c.c.). The acid distillate gave an oily acid (158 mg.), which gave *p*-bromophenacyl *iso*hex-3-enoate, undepressed by the authentic material above. The distillate from the alkaline solution gave *iso*butyraldehyde 2 : 4-dinitrophenylhydrazone (370 mg.). The filtrate from the latter was extracted with benzene as above and chromatographed on alumina, giving acetone 2 : 4-dinitrophenylhydrazone (128 mg.), m. p. 125—126°, undepressed on admixture with authentic material. The residue from the distillation of the *iso*hexenoic acid was extracted with chloroform and identified as humulinic acid, m. p. 93—94°. Light absorption (ethanol) : Max. at 2600, 2680, and 2800 A. with $E^{1\%}_{1cm.}$ = 530, 530, and 460 respectively.

Biological Testing.—The usual " Lab-Lemco "-peptone medium was used for culturing *Staph. aureus*, *M. phlei*, and *B. coli*, and for the lactobacilli standard maltwort of s.g. 1·040 was used (*cf.* Blakebrough,

M.Sc. Thesis, Manchester, 1948). For tests against all organisms, the compounds were dissolved in ethanol (5—10 mg./c.c.) and the required volumes of the solutions added to standard amounts of the media in the usual "series dilution" tests. The *Staphylococcus* and *B. coli* strains were incubated for 18 hours at 36—37°, and *M. phlei* for 48 hours at the same temperature. Incubation of the lactobacilli was effected during 18 hours at 37°, and then at room temperature (25°) for 48 hours.

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382. *The Pigments of "Dragon's Blood" Resin. Part I. Dracorubin.*

By (MRS.) DOROTHY A. COLLINS (née JONES), FRED HAWORTH, KALVA ISARASENA, and ALEXANDER ROBERTSON.

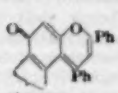
From preliminary experiments on dracorubin, isolated from commercial specimens of "dragon's blood" resin, it is concluded that the compound is an anhydro-2 : 4-diphenylbenzpyranol, $C_{32}H_{24}O_5$, of type (I) derived from the 7-hydroxy-2 : 4-diphenylbenzpyranol, dracorubanol (III; R = H). Contrary to Brockmann and Haase it seems likely that dracorubin contains a methoxyl group but not an active carbonyl group; the oximation product is considered to have a structure of the type (VI). Formed by methylation of dracorubin, *O*-methyldracorubanol (III; R = Me) gave rise to salts with acids and on degradation furnished a product (V; R = Me) identical with the monomethyl ether of draconol (V; R = H) which is obtained by the oxidation of dracorubin with hydrogen peroxide. Dracorubin is represented by the partial formula (I).

FROM "dragon's blood" resin of Indian origin Brockmann and Haase (*Ber.*, 1936, **69**, 1930) isolated the main colouring matter which they named dracorubin and suggested that the compound had the empirical formula $C_{16}H_{14}O_3$. By a somewhat different procedure Hesse (*Annalen*, 1936, **524**, 14) obtained two pigments from the blood-red resin of fruit-bearing parts of the palm *Dracaena Draco Blume* and named the chief compound dracocarmine for which he proposed the formula $C_{31}H_{26}O_5$. For the minor pigment $C_{28}H_{24}O_7$ Hesse proposed the name dracorubin. Subsequently Brockmann and Haase (*Ber.*, 1937, **70**, 1733) re-examined their dracorubin which they found to be lævorotatory; they regarded it as very similar to, if not identical with, Hesse's dracocarmine and, as a result of analyses of the hydrochloride, perchlorate, and picrate, proposed a revised empirical formula $C_{32}H_{24}O_5$. In addition to describing two hydrogenation products Brockmann and Haase showed that on fusion with potassium hydroxide dracorubin gave rise to acetophenone. In a more recent communication which became available to us after the completion of the present work, these authors in collaboration with Freiensehner (*Ber.*, 1944, **77**, 279) have described further degradation experiments on dracorubin, the chief of which is the oxidation of the compound with hydrogen peroxide to give a phenol, draconol $C_{16}H_{10}O_4$, and an acid $C_{16}H_{14}O_3$, for which they tentatively suggest formulæ containing the residue (V; R = H). They consider that dracorubin may be a derivative of anhydro-7-hydroxy-2 : 4-diphenylbenzpyranol substituted in the 5-position by the residue $C_{13}H_{11}O_3$.

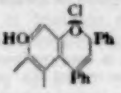
In the course of our preliminary studies* on the colouring matters of "dragon's blood" resin, dracorubin was isolated from a number of samples of commercial resin by a procedure similar to that employed by Brockmann and Haase (*loc. cit.*) and subsequently by their method. The compound was also obtained according to the method employed by Hesse (*loc. cit.*) for the isolation of his dracocarmine. From a comparison of the properties of dracorubin with those of dracocarmine described by Hesse (*loc. cit.*) and of their respective derivatives we consider that dracocarmine and dracorubin are in all probability the same compound (cf. Brockmann and Haase, *loc. cit.*). Further, it has been confirmed that dracorubin is an anhydropyranol base, $C_{32}H_{24}O_5$, of the quinonoid type (I), derived from the carbinol base of type (III; R = H) for which we propose the name dracorubanol. The quinonoid base forms salts by the addition of acids, *e.g.*, with hydrochloric acid it gives the hydrochloride of type (II), *viz.*, dracorubylium chloride. On treatment with sodium acetate this chloride (II) regenerates the parent base (I)

* Our experimental studies on the complex mixture of pigments present in "dragon's blood" resin were undertaken in conjunction with studies on rottlerin and were initiated in 1936 independently of the work of the German authors. The degradation experiments described in the present paper were completed before 1940 and detailed descriptions of them were included in theses presented by my co-workers for higher degrees in the University of Liverpool, *viz.*, Thesis for Degree of Master of Science by Mrs. Dorothy A. Collins (nde Jones) in 1939 and Theses for the Degree of Doctor of Philosophy by Dr. K. Isarasena in 1940 and by Dr. F. Haworth in 1946. A. R.

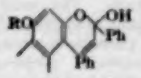
without the formation of the intermediate dracorubanol (III; R = H) (cf. Irvine and Robinson, *J.*, 1927, 2086). In accordance with the established conversion of anhydro-benzpyranols into the methyl ethers of the hydroxybenzpyranols (cf., *e.g.*, Pratt and Robinson, *J.*, 1923, 739, and Robinson and Armit, *J.*, 1925, 1604) methylation of dracorubin with an excess of methyl sulphate and alkali gave rise to optically active (lævorotatory) *O*-methyldracorubanol of type (III; R = Me) from which there were prepared by means of the appropriate acids *O*-methyldracorubylium chloride (IV; R = Cl), picrate (IV; R = $C_6H_2O_7N_3$), perchlorate (IV; R = ClO_4), and ferrichloride (IV; R = $FeCl_4$). In the conversion of optically active dracorubin into *O*-methyldracorubanol a second asymmetric centre is produced at the 2-position and consequently the carbinol base (III; R = Me) (but not the salts) would be expected to exist in two forms capable of being separated by crystallisation, but this has not yet been attempted. The base (III; R = Me) was also prepared by the standard method of Armit and Robinson (*loc. cit.*) for the methylation of anhydro-7-hydroxybenzpyranol, and the methosulphate (IV; R = $MeSO_4$) obtained in red prisms which gave *O*-methyldracorubanol on treatment with aqueous sodium acetate or alkalis. This procedure, however, tended to yield a product contaminated with unchanged dracorubin and was less suitable than the alkali method for the preparation of *O*-methyldracorubanol in quantity.



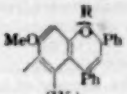
$C_{28}H_{24}(OMe)_2(-O^-)$ (I.)



(II.)



(III.)



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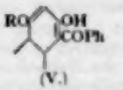

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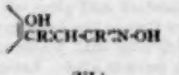

(VI.)

Like Brockmann and Haase (*loc. cit.*) we have found that the application of the standard tests for a methylenedioxy-group to dracorubin gives inconclusive results and we are unable to decide at present whether dracorubin contains this group. Contrary to the views of the German authors, however, we have obtained evidence that dracorubin contains an alkoxyl group, in all probability methoxyl. Although in determinations by the standard micro-Zeisel method dracorubin gave only traces of a volatile iodide, the use of the conditions employed for the estimation of alkylimide groups gave results in agreement with the presence of one methoxyl group (the results obtained by Dr. Ing. A. Schoeller, late of Berlin, and by Mr. R. Rothwell of this laboratory were consistent). In agreement with this view it was found that *O*-methyldracorubanol and *O*-methyldracorubylium ferrichloride gave results indicating the presence of two methoxyl groups. Though it is conceivable that under the conditions employed the alkyl halide might arise by a deep-seated change in the dracorubin molecule, in the absence of concrete evidence for this we regard the compound as containing a methoxyl group. Further, Brockmann and Haase (*loc. cit.*) envisage the possibility of dracorubin containing a keto-group; but although they form colourless products on oximation by the pyridine method we believe that dracorubin and *O*-methyldracorubanol do not contain an active carbonyl group and consider that the oximation products, which give anomalous analytical results (cf. Brockmann and Haase, *loc. cit.*), may be derivatives of the oximes, of type (VI; R = R′ = Ph), of the corresponding styryl ketones obtained by the opening of the oxonium ring. This view is supported by the observation that when flavylium salts are warmed with pyridine–hydroxylamine hydrochloride colourless oximation products are formed which are usually amorphous or resinous. In a favourable case it was found that 8 : 4′-dimethoxyflavylium chloride gave rise to the crystalline oxime, of type (VI; R = H; R′ = C_6H_4·OMe), of 2-hydroxy-*p*-methoxyphenyl 3-methoxystyryl ketone, which on being heated with alcoholic hydrochloric acid regenerated the parent flavylium chloride. Crystalline oximation products were also obtained from anhydro-7-hydroxy-2 : 4-diphenylbenzpyranol and from 7-methoxy-2 : 4-diphenylbenzpyranol or its salts, but these derivatives did not give analytical results in agreement with the values required for the oximes of the corresponding styryl ketones. Like the oximation product from dracorubin the derivative obtained from anhydro-7-hydroxy-2 : 4-diphenylbenzpyranol readily dissolved in dilute aqueous sodium hydroxide.

Of the five oxygen atoms in dracorubin two are present in the anhydrobenzpyranol residue and one probably in a methoxyl group, leaving two unaccounted for. From the properties of dracorubin and of *O*-methyldracorubanol we consider that the two remaining oxygen atoms are present in ether systems.

The degradation of dracorubin with hot alkalis under a variety of conditions gave only benzoic acid and acetophenone in addition to intractable products, whereas oxidation in acetone with aqueous potassium permanganate yielded benzoic acid along with gummy material. In quantitative experiments it was found that the estimation of the phenyl residues from the combined amounts of acetophenone (isolated as the 2 : 4-dinitrophenylhydrazone) and benzoic acid formed with boiling 20% alcoholic potassium hydroxide indicated the presence of more than one phenyl residue in dracorubin, a result in agreement with the Kuhn–Roth estimation given by Brockmann and Haase (*loc. cit.*). Chiefly owing to the insolubility of dracorubin in suitable solvents it was not possible to effect a stepwise oxidative degradation of the base, but with alkaline hydrogen peroxide in methanol we obtained a compound, m. p. 256° (decomp.), which gives a ferric reaction and appears to be identical with the phenol, draconol, described by Brockmann and Haase (*loc. cit.*). On methylation with diazomethane this compound readily gave a monomethyl ether $C_{28}H_{14}O_4(OMe)_2$ (V; R = Me) identical with the phenolic product formed in small yield along with acetophenone by the hydrolytic fission of *O*-methyldracorubanol with alkalis. The same ether was obtained in somewhat better yield when *O*-methyldracorubanol was oxidised in acetone with aqueous potassium permanganate, and the presence of the free phenolic hydroxyl group in it was confirmed by the formation of an acetate and a *p*-nitrobenzoate. Although we have failed to prepare a diagnostic carbonyl derivative, *O*-methyldraconol like draconol gives a ferric reaction in alcohol and therefore appears to contain a carbonyl group in the *ortho*-position to the phenolic hydroxyl group. On hydrogenation with a palladium–charcoal catalyst *O*-methyldraconol gave rise to *O*-methyldihydrodraconol which forms a diacetate and gives an amorphous product with pyridine–*p*-nitrobenzoyl chloride and we consider that in the hydrogenation the >CO group is reduced to >CH(OH). Oxidation of *O*-methyldraconol with potassium permanganate or chromic anhydride gave resinous material along with benzoic acid. Estimated by the Kuhn–Roth method, the amount of benzoic acid obtained from *O*-methyldraconol clearly indicated the presence of one phenyl residue.

In order to clarify the behaviour of dracorubin on methylation by the alkali–methyl sulphate method the application of this reaction to several anhydro-pyranol bases of known structure was studied. In addition to the known bases from 7-hydroxy- and 7-hydroxy-4-phenylflavylium chloride the red crystalline anhydro-pyranols were prepared from 7-hydroxy-6-methyl-, 7-hydroxy-8-methyl-, and 7-hydroxy-5 : 6-dimethyl-flavylium chloride. With the exception of anhydro-7-hydroxy-2 : 4-diphenylbenzpyranol which gave rise to 7-methoxy-2 : 4-diphenylbenzpyranol, the remaining bases furnished only intactable gummy products under the conditions employed in the preparation of *O*-methyldracorubanol, a result which is in keeping with the partial formula (I) for dracorubin.

Experimental.

Dracorubin.—(*a*) The methods originally devised for the isolation of dracorubin were similar to those employed by Brockmann and Haase (*loc. cit.*) and the following modified procedure was ultimately adopted for the preparation of the compound in quantity. The powdered resin (300 g.) was extracted with boiling benzene (2 l.) for 4 hours and the filtered extract was mixed with a solution of picric acid (15 g.) in benzene (130 ml.) and heated under reflux for 6 hours, until the gelatinous brown precipitate, which had separated initially, became granular. Next day the solid (20—25 g.) was collected, washed with benzene (200 ml.), air-dried (with slight darkening), and triturated with a little methanol or alcohol to remove resinous material, leaving the impure picrate as a bright orange powder which did not darken on exposure to air. Decomposition of this product (50 g.) in 95% alcohol (1 l.) with 25% aqueous sodium hydroxide (200 ml.) at room temperature and then at 40° for 1 hour gave crude dracorubin which was collected, well washed with boiling water, and dried; yield, 8 g. of a semi-crystalline, deep scarlet powder. This material was extracted with chloroform, leaving a small amount of a brown residue, the chloroform extract poured on a column of aluminium oxide and, after the lower bluish-purple zone had been washed through the column with much chloroform, the main red zone containing dracorubin was eluted with methanol–chloroform (1 : 9). Concentration of the red solution in a vacuum gave crystalline dracorubin which was purified by repeated chromatography on aluminium oxide to remove trades of accompanying pigments: yield, 150 g. of pure dracorubin from 15 kg. of resin. Crystallised from benzene and then benzene–methanol (1 : 9), dracorubin was obtained in dark red plates, m. p. 315°, having a greenish-golden reflex (Found, in a specimen dried in a high vacuum at 90°: C, 78·6; H, 4·9; OMe, 6·2. Calc. for $C_{31}H_{21}O_4$·OMe, C, 78·7; H, 5·0; OMe, 6·2%). Purified from chloroform, the compound formed dark red prisms, m. p. 315°, containing solvent of crystallisation which was not completely removed when a specimen was dried in a high vacuum at 90° (Found, in a dried sample: Cl, 1·5%). The m. p. of dracorubin varies somewhat with the rate of heating. On

being slowly heated it melts at 299° but placed in a bath at 250—300° and rapidly heated the compound has been found to melt invariably at 315°.

(*b*) A specimen of dracorubin was isolated according to the method employed by Hesse (*loc. cit.*) for dracocarmine and, on repeated purification by chromatography with aluminium oxide followed by recrystallisation from benzene, had m. p. 315° (rapid heating) and was identical in every way with a specimen isolated by method (*a*) (Found, in a specimen dried in a high vacuum at 90°: C, 78·4; H, 5·0%).

Dracorubin (1 g.) was heated with hydroxylamine hydrochloride (1 g.) in pyridine (60 ml.) on the steam-bath for 6 hours and the resulting almost colourless solution poured on ice (200 g.). Next day the solid was collected and repeatedly crystallised from moist acetone, giving a *compound* in colourless needles which charred at 220° after becoming pink at 190° and was readily soluble in dilute aqueous sodium hydroxide (Found, in material dried in a high vacuum at 100°: C, 73·4; H, 5·4; N, 3·0. $C_{32}H_{27}O_6N$ requires C, 73·7; H, 5·2; N, 2·7%. $C_{32}H_{31}O_6N$ requires C, 76·3; H, 5·0; N, 2·8%). This product, which had a negative ferric reaction, separated from chloroform or aqueous alcohol in colourless rectangular plates and on being boiled with 2*N*-hydrochloric acid gave rise to dracorubylium chloride which, on treatment with aqueous sodium hydroxide, regenerated dracorubin.

Dracorubylium Salts.—(*a*) When a solution of the dracorubin (0·1 g.) in ethyl acetate (80 ml.) was saturated with hydrogen chloride an almost theoretical yield of dracorubylium chloride separated in reddish-orange needles. Recrystallised from a mixture of 10% hydrochloric acid and methanol or alcohol, the chloride formed slender orange-red needles, readily soluble in acetic acid, moderately soluble in carbon tetrachloride, benzene, or ethyl acetate (Found: C, 73·2; H, 4·9; Cl, 6·7. Calc. for $C_{32}H_{31}O_6Cl$: C, 73·2; H, 4·8; Cl, 6·8%). The chloride slowly decomposes in moist air with loss of some hydrogen chloride and readily regenerates dracorubin on treatment with aqueous sodium acetate or with much water.

(*b*) A warm saturated solution of dracorubin in ethyl acetate (40 ml.) was mixed with an excess of 30% perchloric acid and the resulting precipitate collected, washed with ethyl acetate, and crystallised from acetic acid, giving dracorubylium perchlorate in clusters of orange needles, m. p. 291° (decomp.) after sintering at 259°, identical with a specimen prepared from the chloride (Found: C, 65·4; H, 4·3; Cl, 6·1. Calc. for $C_{32}H_{31}O_6Cl$: C, 65·3; H, 4·4; Cl, 6·0%). This salt is much more stable than the chloride but on treatment with aqueous-alcoholic sodium acetate it regnerates dracorubin.

(*c*) The addition of picric acid (0·2 g.) in benzene (5 ml.) to a saturated solution of dracorubin (0·25 g.) in warm methanol–benzene (1 : 9) gave dracorubylium picrate which separated from methanol or acetic acid in slender yellow needles, decomposing at 260° (Found: C, 63·5; H, 3·9; N, 5·9. Calc. for $C_{38}H_{27}O_{13}N_3$: C, 63·6; H, 3·8; N, 5·9%).

(*d*) A solution of dracorubylium chloride (0·5 g.) in the minimum amount of acetic acid at 30° was treated with an excess of a concentrated solution of ferric chloride in concentrated hydrochloric acid, and the buff-coloured precipitate collected, washed with a little acetic acid, and dried in the air. Crystallised from acetic acid containing a little formic acid, the solid gave a substance which does not appear to be a normal ferrichloride (Found, in a specimen dried in a high vacuum at 80°: C, 56·8; H, 4·6. Calc. for $C_{32}H_{31}O_6Cl_4Fe$: C, 55·9; H, 3·7%). This product is sparingly soluble in chloroform or ethyl acetate and somewhat more soluble in methanol or alcohol.

O-Methyldracorubanol (III; R = Me).—To a vigorously agitated solution of dracorubin (5 g.) in a mixture of methanol (100 ml.) and methyl sulphate (200 ml.), 20% aqueous sodium hydroxide was added gradually at a rate sufficient to maintain the temperature of the mixture at about 70°. When the reaction mixture became permanently alkaline, indicated at this stage by the appearance of a red colour, a further portion of methyl sulphate (100 ml.) was added, followed by more 20% aqueous sodium hydroxide until the mixture again became alkaline. This procedure was repeated until an almost colourless insoluble product was separated. The mixture was then diluted with water (about 2 l.) and next day the pale brown, almost colourless solid was collected, washed, and dried. Sufficient *N*-sodium hydroxide was added to the yellow solution of this product in the minimum amount of methanol necessary to discharge the colour (due to traces of acid) and to precipitate the crude *O-methyldracorubanol* (4·5 g.) which was collected, well washed with water, dried, and crystallised from aqueous acetone and then from benzene–light petroleum (b. p. 60—80°), forming masses of colourless slender needles, m. p. 203°, after slight darkening at 180°, $[\alpha]_D^{18}$ −119·0° in chloroform (*c*, 0·4 g.) (Found, in a specimen dried in a high vacuum at 90°: C, 76·2; H, 5·5; OMe, 12·6. $C_{31}H_{28}O_4(OMe)_4$ requires C, 76·2; H, 5·4; OMe, 11·9%). This compound, which is readily soluble in pyridine or acetone and moderately soluble in methanol or alcohol, quickly absorbs acidic vapours when exposed to the atmosphere and becomes yellow. On being heated with hydroxylamine hydrochloride and pyridine on the steam-bath for 6 hours *O*-methyldracorubanol gave a *product* which separated from aqueous pyridine in long colourless needles, m. p. 285° (decomp.) (Found: C, 74·0; H, 5·4; N, 5·2. $C_{32}H_{33}O_6N$ requires C, 74·0; H, 5·4; N, 2·6%). When the hydroxylamine hydrochloride was replaced by semicarbazide hydrochloride in this experiment a *compound* was obtained which formed small colourless prisms, m. p. 210° (decomp.), from aqueous pyridine or acetone (Found: C, 69·5; H, 5·3; N, 6·7. $C_{34}H_{31}O_6N_3$ requires C, 70·7; H, 5·4; N, 7·3%).

O-Methyldracorubylium Chloride (IV; R = Cl).—This salt was prepared quantitatively by the addition of an excess of 2*N*-hydrochloric acid to *O*-methyldracorubanol (0·5 g.) in acetic acid (50 ml.). Crystallised from dilute hydrochloric acid or dilute hydrochloric acid–acetic acid (2 : 1), the *chloride* formed long orange needles which began to decompose at 260° and finally fused at about 280° (Found: C, 73·0; H, 5·2; Cl, 6·4. $C_{32}H_{27}O_4Cl$ requires C, 73·5; H, 5·1; Cl, 6·6%). This compound is readily soluble in acetic acid, methanol, ethanol, or chloroform and, on treatment with aqueous sodium acetate or sodium hydroxide, regenerates the carbinol base.

Treatment of *O*-methyldracorubanol, dissolved in the minimum amount of acetic acid, with an excess of aqueous alcoholic picric acid gave an almost theoretical yield of the *picrate* (IV; R = $C_6H_2O_7N_3$) which is remarkably stable and crystallised from acetic acid as well as alcohol or ethyl acetate in long orange needles, m. p. 203° (decomp.) after darkening at 140° (Found: C, 64·1; H, 4·1; N, 5·8. $C_{38}H_{29}O_{13}N_3$ requires C, 64·0; H, 4·0; N, 5·7%).

The addition of a solution of ferric chloride in concentrated hydrochloric acid to *O*-methyldracorubanol or its chloride in a little acetic acid precipitated *O-methyldracorubylium ferrichloride* (IV; R = $FeCl_4$) which separated from formic or acetic acid in orange-red needles, m. p. 190° (decomp.) [Found: C, 56·6; H, 4·1; OMe, 10·5; Fe, 7·7. $C_{31}H_{31}O_5Cl_4Fe(OMe)_3$ requires C, 56·5; H, 3·9; OMe, 8·9; Fe, 8·0%].

O-Methyldracorubylium perchlorate (IV; R = ClO_4) separated from acetic acid in slender orange needles, m. p. 284—285° (decomp.) [Found: C, 65·4; H, 4·6; Cl, 6·0. $C_{32}H_{31}O_9Cl$ requires C, 65·7; H, 4·5; Cl, 5·9%].

Dracenol (V; R = H).—A solution of dracorubin (0·25 g.) in methanol (60 ml.) was mixed with 15% hydrogen peroxide (1·5 ml.) and 2*N*-aqueous sodium hydroxide (25 ml.). The deep red colour of the mixture changed to yellow and, on acidification with acetic acid, a yellow solid separated. Crystallised from dilute ethanol, this compound formed yellow prisms, m. p. 256° (decomp.), soluble in methanol, chloroform, or pyridine and giving a brownish-green ferric reaction in alcohol. Owing to the tendency of this compound to retain solvent of crystallisation consistent analytical results were not obtained (*cf.* Brockmann and Haase, *loc. cit.*). Methylation of this phenol with diazomethane in ether–chloroform, however, gave *O*-methyldracenol which formed slender, pale yellow needles, m. p. 247°, from ethyl acetate and was identical with a specimen obtained from *O*-methyldracorubanol.

Degradation of O-Methyldracorubanol.—(*a*) A solution of the compound (0·5 g.) in alcohol (100 ml.) containing potassium hydroxide (5 g. in water 5 ml.) was evaporated and the residue heated to 240° (metal-bath) for 10 minutes. After having been washed with a little ether the cooled melt was dissolved in water at 0°, and the solution was acidified with concentrated hydrochloric acid (added drop-wise with cooling) and repeatedly extracted with ether. From the combined ethereal extracts a little benzoic acid was isolated by means of aqueous sodium hydrogen carbonate. Subsequent evaporation of the dried extracts then left a small amount of *O-methyldracenol* which separated from warm acetone, ethyl acetate, or acetic acid in pale yellow slender needles, m. p. 247°, sparingly soluble in the usual organic solvents in the cold except pyridine, insoluble in dilute aqueous sodium hydroxide, and having a brownish-green ferric reaction in alcohol [Found: C, 71·8; H, 5·4; OMe, 14·1; *M*, 382. $C_{28}H_{16}O_4(OMe)_2$ requires C, 71·8; H, 5·3; OMe, 14·8%; *M*, 418. Calc. for $C_{26}H_{16}O_3(OMe)_4$: C, 72·0; H, 5·2; OMe, 17·7%; *M*, 352]. With alcoholic sodium hydroxide this ether forms a sparingly soluble yellow sodium salt.

Evaporation of the ethereal washings of the potassium hydroxide melt left a small amount of acetophenone which was identified by conversion into the 2 : 4-dinitrophenylhydrazone, m. p. 237° after purification.

(*b*) 3% Aqueous potassium permanganate (100 ml.) was added drop-wise to a solution of *O*-methyldracorubanol (1 g.) in boiling acetone (200 ml.) during 1½ hours. Next day the mixture was cleared with the minimum amount of sulphur dioxide and diluted with water (100 ml.), the acetone was allowed to evaporate spontaneously, and the pale yellow solid collected. A further small amount of the same product mixed with benzoic acid was obtained after extraction of the filtrate with ether in a continuous extractor for 30 hours. Crystallisation of the combined solids from acetone gave *O*-methyldracenol (0·1 g.), m. p. and mixed m. p. 247°, identical with a specimen obtained by method (*a*). With methanolic sodium methoxide this compound furnished a canary-yellow precipitate of the sodium derivative from which the phenol was readily regenerated on treatment with acid. Acetylation of this phenol (1 g.) with pyridine (5 ml.) and acetic anhydride (10 ml.) on the steam-bath for 6 hours gave a product which was difficult to purify. Repeated crystallisation of the material alternately from ethyl acetate, acetone, and methanol–chloroform ultimately furnished the *acetate* in colourless rhombic plates (0·4 g.), m. p. 243° (Found, in a specimen dried in a high vacuum at 60°: C, 70·0; H, 5·3. $C_{31}H_{24}O_7$ requires C, 70·4; H, 5·0%. $C_{30}H_{22}O_6$ requires C, 70·4; H, 5·1%). A mixture of the yellow sodium salt of *O*-methyldracenol (0·1 g.), *p*-nitrobenzoyl chloride (0·1 g.), and toluene (30 ml.) was agitated for 10 minutes and then heated on the steam-bath for ½ hour. The solid which separated from the cooled mixture was washed with water, dried, and crystallised from pyridine, giving the *p-nitrobenzoate* in rosettes of small, almost colourless needles, m. p. 307° (decomp.) (Found, in a dried specimen: C, 67·7; H, 4·5; N, 2·7. $C_{33}H_{23}O_8N$ requires C, 67·7; H, 4·4; N, 2·5%).

Oxidation of *O*-methyldracenol (0·5 g.) in boiling acetone (450 ml.) with saturated aqueous potassium permanganate (150 ml., added dropwise) gave rise to benzoic acid (about 0·02 g.) along with unchanged phenol (0·87 g.) and a small amount of yellow amorphous product. Oxidation of the phenol (0·6 g.) with 5*N*-chromic acid (40 ml.) and concentrated sulphuric acid on the steam-bath for 1 hour yielded benzoic acid which was isolated with ether and purified by crystallisation from light petroleum (yield, 0·15 g. of benzoic acid; theory for 1 phenyl residue in *O*-methyldracenol is 0·21 g.).

Hydrogenation of O-Methyldracenol.—A solution of the compound (1 g.) in acetic acid (150 ml.) at 100° was agitated with hydrogen and a palladium–charcoal catalyst (from 5 g. of charcoal and 0·2 g. of palladium chloride) for 1 hour, filtered (wash charcoal with acetic acid), and evaporated in a vacuum. Crystallised from ethyl acetate and then acetone or toluene, the residue gave the *dihydro*-derivative in pale yellow rhombic plates (0·6 g.), m. p. 221°, soluble in alcohol or chloroform and having a bottle-green ferric reaction in alcohol [Found: C, 71·5; H, 5·8; OMe, 14·1. $C_{28}H_{18}O_4(OMe)_2$ requires C, 71·4; H, 5·7; OMe, 14·7%]. Acetylation of this compound by the pyridine method on the steam-bath for 6 hours gave rise to the *diacetate* which was repeatedly recrystallised from dilute acetone, alcohol, and then ethyl acetate, forming colourless diamond-shaped prisms, m. p. 218° [Found: C, 69·3; H, 5·5. $C_{32}H_{24}O_8$ (diacetate) requires C, 69·1; H, 5·6%. Calc. for $C_{27}H_{22}O_7$ (mono-acetate): C, 70·1; H, 5·6%].

[With J. H. Richards] *Oximation of 8 : 4′-Dimethoxyflavylium Chloride.*—The chloride was prepared by the condensation of *p*-methoxyacetophenone (2 g.) and *o*-vanillin (2 g.) with hydrogen chloride–ethyl acetate and formed stellate clusters of orange-brown needles from 4% hydrochloric acid (*cf.* Robinson *et al.*, *J.*, 1924, 207).

A solution of this chloride (2 g.) and hydroxylamine hydrochloride (1 g.) in pyridine (15 ml.) was warmed on the steam-bath for 6 hours and next day the pale yellow mixture was poured on crushed ice. Crystallisation of the colourless precipitate from alcohol gave the *oxime* of 2-hydroxy-3-methoxystyryl

4-methoxyphenyl ketone in colourless slender needles, m. p. 148° (decomp.) (Found: C, 68·2; H, 5·9; N, 4·9. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7; N, 4·7%). This compound (0·2 g.) was heated on the steam-bath with a mixture of concentrated hydrochloric acid (10 ml.) and alcohol (10 ml.) for 45 minutes and the dark red solution treated with an excess of ferric chloride in concentrated hydrochloric acid. Crystallised from acetic acid, the resulting solid gave the 8 : 4'-dimethoxyflavylium ferrichloride in brown needles with an orange sheen, m. p. 178°, identical with an authentic specimen which we have invariably found to have m. p. 178° (Found: C, 44·1; H, 3·2; Fe, 11·9. Calc. for $C_{17}H_{15}O_4Cl_4Fe$: C, 43·9; H, 3·2; Fe, 12·0%) (compare Robinson *et al.*, *loc. cit.*, who give m. p. 180°).

7-Methoxy-6-methylflavylium Chloride.—The interaction of 5-methylresorcylaldehyde (7 g.) and acetophenone (8 ml.) in ethyl acetate (200 ml.) saturated with hydrogen chloride furnished 7-hydroxy-6-methylflavylium chloride. Crystallised from 10% and then 5% hydrochloric acid, this salt was obtained as a *hydrate* in brownish-yellow needles (8 g.), m. p. 162° (decomp.), with a greenish-yellow reflex which was partly dehydrated on being dried at room temperature (Found, in a specimen dried in a vacuum over potassium hydroxide: C, 69·3; H, 5·0. $C_{16}H_{13}O_2Cl,0{\cdot}25H_2O$ requires C, 69·3; H, 4·9%).

Methylation of 2 : 4-dihydroxy-5-methylbenzaldehyde (10 g.) with methyl iodide (12 g.) and potassium carbonate (15 g.) in boiling acetone (200 ml.) during 80 minutes gave rise to *2-hydroxy-4-methoxy-5-methylbenzaldehyde* which formed needles (9 g.), m. p. 72°, from dilute methanol, having a violet ferric reaction [Found: C, 65·2; H, 6·3; OMe, 18·8. $C_9H_{10}O_3$(OMe) requires C, 65·1; H, 6·0; OMe, 18·7%]. The condensation of this aldehyde (2·5 g.) with acetophenone (2·5 ml.) in ethyl acetate with hydrogen chloride furnished *7-methoxy-6-methylflavylium chloride* which formed orange-yellow needles (3·5 g.), m. p. 174° (decomp.), from 2*N*-hydrochloric acid (Found: C, 71·4; H, 5·4. $C_{17}H_{15}O_2Cl$ requires C, 71·2; H, 5·2%). The *perchlorate* separated from acetic acid in deep orange-yellow needles (Found: C, 58·0; H, 4·3. $C_{17}H_{15}O_6Cl$ requires C, 58·2; H, 4·3%).

7-Hydroxy-8-methylflavylium chloride was prepared from 2 : 4-dihydroxy-3-methylbenzaldehyde and acetophenone by means of ethyl acetate–hydrogen chloride and crystallised from 10% hydrochloric acid, forming red needles decomposing at 127° (Found: C, 70·7; H, 4·9. $C_{16}H_{13}O_2Cl$ requires C, 70·5; H, 4·8%). The perchlorate separated from acetic acid in purple needles, m. p. 187° (decomp.). Prepared in the usual way, the anhydro-base crystallised from *n*-amyl alcohol in scarlet needles, m. p. 149° (decomp.), readily soluble in methanol, alcohol, benzene, or chloroform.

7-Hydroxy-5 : 6-dimethylflavylium Perchlorate.—7-Hydroxy-5 : 6-dimethylflavylium chloride was prepared from 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde (Robertson and Whalley, *J.*, 1949, 3038) and acetophenone and crystallised from 10% hydrochloric acid, forming small yellow needles, m. p. 204—206° (decomp.). The *perchlorate* separated from acetic acid in reddish-brown needles (Found: C, 57·5; H, 4·6. $C_{17}H_{15}O_6Cl$ requires C, 58·2; H, 4·3%).

Treatment of an aqueous-methanolic solution of the chloride with aqueous sodium acetate gave the anhydro-base which was crystallised from *n*-amyl alcohol and then from chloroform–benzene, forming deep-red needles, m. p. 166° (decomp.), readily soluble in alcohol, chloroform, or pyridine.

Oximation and Methylation of Anhydro-7-hydroxy-2 : 4-diphenylbenzpyranol.—Formed from 7-hydroxy-4-phenylflavylium chloride (Bülow and Sickerer, *Ber.*, 1901, **34**, 2368), *7-hydroxy-4-phenylflavylium perchlorate* separated from acetic acid in small orange prisms, m. p. 260—262° (decomp.), having a lilac reflex (Found: C, 63·2; H, 3·8. $C_{21}H_{15}O_6Cl$ requires C, 63·3; H, 3·8%).

When a mixture of this anhydro-pyranol (Bülow and Sickerer, *loc. cit.*) (1 g.) was heated on the steam-bath with hydroxylamine hydrochloride (1·5 g.), and pyridine (15 ml.), the solution quickly became colourless and after 4 hours a test-sample on acidification and subsequent treatment with sodium acetate did not give unchanged quinonoid base. The mixture was then diluted with water and acidified with acetic acid, and the resulting viscous product was triturated with dilute acetic acid until it solidified. Crystallised from alcohol, this material gave a *substance* in clusters of colourless tiny prisms, m. p. 176° (decomp.) after sintering at 78°, which was readily soluble in dilute aqueous sodium hydroxide (Found, in material dried in a high vacuum at 60°: C, 75·4; H, 5·2; N, 7·8. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·2; N, 4·2%).

On methylation with methyl sulphate and aqueous sodium hydroxide by the procedure employed for dracorubin anhydro-7-hydroxy-2 : 4-diphenylbenzypyranol gave an almost theoretical yield of a resinous product which was purified by conversion into 7-methoxy-4-phenylflavylium chloride. This compound separated from dilute alcohol in long orange-yellow needles which on treatment with aqueous sodium acetate furnished a gum which solidified on trituration with water and then aqueous acetone, and on crystallisation from 50% acetone gave rise to 7-methoxy-2 : 4-diphenylbenzpyranol in colourless elongated small prisms, m. p. 117° (Found, in a specimen dried in a high vacuum at 60°: C, 80·0; H, 5·5%) (cf. Robinson and Turner, *J.*, 1918, **874**, who gave m. p. 55—57° for the amorphous compound). Crystallisation of the pyranol from dilute alcohol gave a mixed product in tiny colourless plates which partly melted at 85°. On one occasion the crude methylation product was repeatedly crystallised from methanol, giving the methyl ether of 7-methoxy-2 : 4-diphenylbenzpyranol in colourless elongated prisms, m. p. 116°, which became yellow on exposure to the laboratory atmosphere [Found: C, 79·8; H, 5·7; OMe, 16·7. Calc. for $C_{21}H_{14}O$(OMe)$_2$: C, 80·2; H, 5·8; OMe, 18·0%] (cf. Bülow and Sickerer, *loc. cit.*, who give m. p. 104° and Brockmann and Junge, *Ber.*, 1944, **77**, *B*, 44, who give m. p. 114°). Prepared from the pyranol, 7-methoxy-2-phenylflavylium ferrichloride formed elongated orange prisms, m. p. 191° (Armit and Robinson, *loc. cit.*), and the perchlorate formed orange-yellow needles, m. p. 238° (Kehrmann and Reider, *Helv. Chim. Acta*, 1926, **9**, 491).

Oximation of the 7-methoxy-2 : 4-diphenylbenzpyranol or of 7-methoxy-4-phenylflavylium chloride with pyridine-hydroxylamine hydrochloride on the steam-bath for 4 hours gave a *substance* which, on trituration with water followed by crystallisation from alcohol, formed tiny colourless plates, m. p. 164° (Found, in a specimen dried in a high vacuum at 80°: C, 76·7; H, 5·5; N, 7·3. $C_{22}H_{19}O_3N$ requires C, 76·5; H, 5·2; N, 4·1%).

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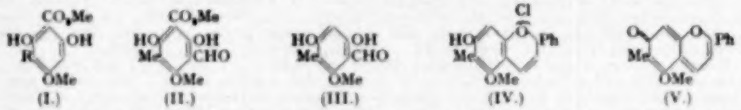
383. *The Pigments of "Dragon's Blood" Resin. Part II. A Synthesis of Dracorhodin.*

By Alexander Robertson and W. B. Whalley.

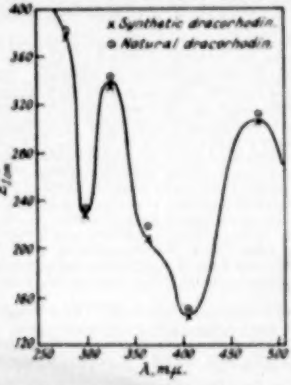
The constitution (V) assigned to dracorhodin by Brockmann and Junge has been confirmed by a synthesis of the compound starting from acetophenone and 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde (III) which has been prepared by a novel route.

From the alkaline liquor left on the decomposition of crude dracorubin picrate with aqueous sodium hydroxide Brockmann and Junge (*Ber.*, 1943, **76**, 751) isolated dracorhodin, a minor pigment of "dragon's blood" resin which they recognised to be an anhydropyranol base. On hydrolytic fission this compound gave rise to 2-methylphloroglucinol 3-methyl ether along with acetophenone and was isomeric with the anhydro-base from synthetical 5-hydroxy-7-methoxy-8-methyl- and from 5-hydroxy-7-methoxy-6-methyl-flavylium chloride. These results and studies on the anhydro-bases derived from 5- and 7-hydroxyflavylium salts (cf. subsequent work of Brockmann, Junge, and Eckhardt, *Ber.*, 1944, **77**, 347) led the authors to conclude that dracorhodin had formula (V). By the condensation of 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde and acetophenone according to the standard procedure Brockmann and Junge (*loc. cit.*) obtained a product in insufficient quantity for purification and analysis but from an examination of its ultra-violet absorption spectrum within a restricted range of wave-lengths they concluded that their synthetical material contained dracorhodin. The aldehydic component, m. p. 163—164°, employed by these authors in this synthesis, was obtained as a by-product in the preparation of 2 : 6-dihydroxy-4-methoxy-3-methylbenzaldehyde from 2-methylphloroglucinol 3-methyl ether by the method of Gattermann and appears to have been impure. Accordingly, in view of its possible relation to dracorubin, the main pigment of "dragon's blood" resin, it seemed desirable to confirm the structure of dracorhodin by an unequivocal synthesis. Small specimens of dracorhodin were isolated from "dragon's blood" resin in these laboratories during 1944 by Dr. F. Haworth (unpublished work; see also Part I, preceding paper) and had properties identical with those described by the German authors.



(I.) (II.) (III.) (IV.) (V.)

In a prolonged search for a satisfactory route to the intermediate 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde (III) required for the synthesis of dracorhodin it was ultimately discovered that this aldehyde could be obtained in good yield by the hydrolysis of the anil of methyl 2 : 6-dihydroxy-4-methoxy-3-formyl-5-methylbenzoate (II) with simultaneous decarboxylation of the resulting acid. All attempts to hydrolyse the parent formyl derivative (II) to (III) were unsuccessful. The intermediate ester (I; R = Me) required for the preparation of (II) has been obtained in good yield by the Clemmensen reduction of (I; R = CHO) in methanol, a route which is superior to that described by Herzig and Wenzel (*Monatsh.*, 1902, **23**, 113).



The condensation of the aldehyde (III) and acetophenone with hydrogen chloride to give (IV) did not proceed smoothly and the results depend greatly on the solvent employed. In methanol the main product appears to be a red substance which may be a xanthylium salt and this is formed, to a small extent, even in acetic acid which was found to be the most satisfactory medium. Thus prepared, 7-hydroxy-5-methoxy-6-methylflavylium chloride (IV) was identical with the hydrochloride of natural dracorhodin and on treatment with aqueous sodium acetate or sodium carbonate gave the anhydro-base (V), identical with the natural compound. The identity of natural and

synthetical dracorhodin was confirmed by examination of their absorption spectra and by comparison of their respective picrates and perchlorates. The absorption curves for synthetical and natural dracorhodin were coincidental within the limits of experimental error, and the curve for the natural base only is reproduced (see figure).

Dracorhodin.		Minima.		Inflexions.		Maxima.	
Natural	λ, mμ.	298·0	402·0	283·0	367·0	324·5	480·0
	$E^{1\%}_{1cm.}$	227	154	374	222·2	349	317·5
Synthetic	λ, mμ.	298·0	401·0	282	368·5	325·0	479·0
	$E^{1\%}_{1cm.}$	230	150	379	210	335	310

Experimental.

Methyl 2 : 6-*Dihydroxy*-4-*methoxy*-3-*methylbenzoate* (I; R = Me).—Methyl 2 : 6-dihydroxy-4-methoxy-3-formylbenzoate (I; R = CHO), m. p. 177·5°, was prepared by the following modification of the method described by Clarke, Glaser, and Robertson (*J.*, 1948, 2260). A solution of methyl 2 : 6-dihydroxy-4-methoxybenzoate (I; R = H) (6·2 g.) and hydrogen cyanide (15 ml.) in ether (225 ml.) was saturated at 0° with hydrogen chloride and 24 hours later the copious, colourless precipitate was washed with ether and heated with water to 100°. The solid dissolved and was replaced by the formyl derivative which separated almost quantitatively when the hydrolysate was cooled. The crude compound (5·6 g.) had m. p. 176°.

A solution of the foregoing formyl derivative (I; R = CHO) (6·5 g.) in methanol (250 ml.) was added during 20 minutes to concentrated hydrochloric acid (80 ml.) and water (20 ml.) containing amalgamated zinc (80 g.), and the reaction completed by heating the mixture under reflux for 10 minutes. The hot liquid was then decanted, the residual amalgam was washed with hot methanol (100 ml.), and the combined liquor and washings were diluted with water (300 ml.). On cooling, the mixture deposited methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (I; R = Me) in colourless needles (5·2 g.), m. p. 132—133°, unchanged on recrystallisation from aqueous methanol from which it separated in colourless rectangular plates (cf. Herzig and Wenzel, *loc. cit.*).

2 : 4-*Dihydroxy*-6-*methoxy*-5-*methylbenzaldehyde* (III).—The interaction of methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (3 g.) (I; R = Me) with hydrogen cyanide (5 ml.) and zinc cyanide (5 g.) in ether saturated at 0° with hydrogen chloride gave a colourless crystalline solid together with a small amount of an oil. This product was isolated 24 hours later, washed with ether, and dissolved in water (150 ml.). The solution was rapidly heated to boiling and, on cooling, deposited *methyl* 2 : 6-*dihydroxy*-4-*methoxy*-3-*formyl*-5-*methylbenzoate* (II) in almost colourless plates (1·5 g.). Recrystallised from light petroleum or methanol, this compound formed long, slender, colourless needles, m. p. 122°, which in contact with the mother-liquor changed into stout colourless prisms, m. p. 122° (Found: C, 55·3; H, 5·2. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%), having a red-brown ferric reaction in alcohol. The aldehydo-ester, which is readily soluble in acetone, moderately soluble in alcohol, and sparingly soluble in light petroleum, sublimes at 120°/0·1 mm., forming clusters of stout needles.

When the ethereal mother-liquors from the aldimine derivative were mixed with more hydrogen cyanide (5 ml.) and zinc cyanide (3 g.) and again saturated with hydrogen chloride, a further quantity of the aldimine complex was obtained which gave the aldehyde (0·7 g.).

Prepared by heating a mixture of the aldehydo-ester (II) (5 g.) and aniline (2·5 g.) in methanol (100 ml.) on the steam-bath for 5 minutes, the *anil* crystallised from methanol in clusters of lemon-yellow needles (5·5 g.), m. p. 162° (Found: N, 4·6. $C_{17}H_{17}O_5N$ requires N, 4·4%). When a solution of this anil (1 g.) in 10% aqueous sodium hydroxide (25 ml.) was heated under reflux in an atmosphere of nitrogen for 2 hours, cooled, and acidified with concentrated hydrochloric acid, 4 : 6-*dihydroxy*-2-*methoxy*-3-*methylbenzaldehyde* (III) separated as a pale fawn-coloured crystalline solid, m. p. 170—172°, which, on recrystallisation from benzene–light petroleum or aqueous methanol, formed slender colourless prisms (0·4 g.), m. p. 175° (Found: C, 59·5; H, 5·6. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%) (cf. Brockmann and Junge, *loc. cit.*, who gave m. p. 163—164°). The aldehyde, which has a red-brown ferric reaction in alcohol, is readily soluble in alcohol, acetone, or benzene and sparingly soluble in light petroleum. The *anil* separated from aqueous methanol in clusters of orange needles, m. p. 160° (decomp.) (Found: N, 5·4. $C_{16}H_{15}O_4N$ requires N, 5·4%), and the 2 : 4-*dinitrophenylhydrazone* formed tiny, deep-scarlet, shining prisms, m. p. 294—295° (decomp.), from ethyl acetate (Found: N, 15·2. $C_{15}H_{14}O_8N_4$ requires N, 15·5%) (cf. Brockmann and Junge, *loc. cit.*, who give m. p. 245—247°).

Dracorhodin (V).—A stream of hydrogen chloride was led into a solution of 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde (0·5 g.) and acetophenone (1·3 g.) in acetic acid (5 ml.) for 1 hour, and 24 hours later the golden-orange crystalline product was collected, washed with ether, and crystallised from 2*N*-hydrochloric acid, giving 7-hydroxy-5-methoxy-6-methylflavylium chloride (IV) as a *hydrate* in golden-brown needles, m. p. 205° (decomp.) after darkening at about 180° (Found: C, 63·3; H, 5·9; Cl, 10·8. $C_{17}H_{15}O_5Cl,H_2O$ requires C, 63·7; H, 5·3; Cl, 11·1%). Obtained from (IV) by means of aqueous sodium acetate or sodium hydrogen carbonate, dracorhodin separated from aqueous methanol in rosettes of deep-red prisms having a green reflex, m. p. 169° (decomp.), undepressed on admixture with a natural specimen (Found: C, 77·0; H, 5·5. Calc. for $C_{17}H_{14}O_5$: C, 76·6; H, 5·3%). The picrate crystallised from methanol containing a little picric acid in slender golden-brown needles, m. p. 217—220° (decomp.), alone or admixed with a specimen prepared from natural dracorhodin (Found: C, 55·6; H, 3·6; N, 8·7. Calc. for $C_{23}H_{17}O_{12}N_3$: C, 55·8; H, 3·4; N, 8·4%). Crystallised from methanol containing a trace of perchloric acid, 7-hydroxy-5-methoxy-6-methylflavylium perchlorate formed irregular golden-brown prisms, m. p. 227—230° (decomp.), the properties of which are identical with those of the natural derivative (Found: C, 55·5; H, 4·3; Cl, 10·4. Calc. for $C_{17}H_{15}O_7Cl$: C, 55·7; H, 4·1; Cl, 9·7%) [cf. Brockmann and Junge, *loc. cit.*, who give m. p. 233—236° (decomp.)].

Natural dracorhodin was isolated from the requisite fraction obtained during the isolation of dracorubin and converted into the picrate which on repeated recrystallisation from methanol containing a little picric acid had m. p. 217—220° (decomp.) (Found : C, 55·9; H, 3·6; N, 8·2%). Regenerated from the picrate, dracorhodin separated from aqueous methanol in rosettes of deep-crimson prisms, m. p. 169° (decomp.), having a green reflex.

The ultra-violet absorption spectra were determined with a Beckman quartz spectrophotometer in benzene solution by the courtesy of Professor R. A. Morton of the Biochemistry Department to whom we express our thanks.

UNIVERSITY OF LIVERPOOL. [*Received, April* 3*rd*, 1950.]

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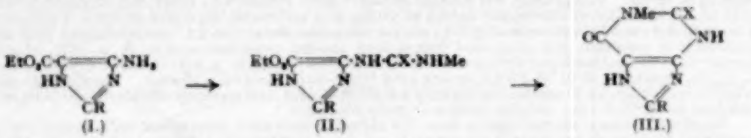
384. *Studies in the Azole Series. Part XXIX. The Preparation of Some Natural Xanthines and Related Purines.*

By A. H. COOK and G. H. THOMAS.

Ethyl 4-aminoglyoxaline-5-carboxylate on reaction with methyl *iso*cyanate followed by treatment with alkali affords 1-methylxanthine. Methylation of the glyoxaline with diazomethane yields a monomethyl derivative orientated so as to give paraxanthine and caffeine by the usual pyrimidine cyclisation. Ethyl 4-amino-2-phenyl- and -2-benzyl-glyoxaline-5-carboxylate likewise form monomethyl derivatives from which, ultimately, are obtained 8-*phenyl*- and 8-*benzyl-caffeine*. Reaction of aminoglyoxalines with urea yields, with some difficulty, xanthines substituted only at $C_{(8)}$. Thiourea reacts only very slowly with aminoglyoxalines but acetyl *iso*thiocyanate is an excellent substitute.

COOK, DAVIS, HEILBRON, AND THOMAS (Part XIV of this series, *J.*, 1949, 1071) described a synthesis of xanthines whereby ethyl 4-aminoglyoxaline-5-carboxylates (I; R = H, Me, Ph, and CH_2Ph) reacted with methyl *iso*thiocyanate, and the resulting 4-*N*-methylthioureido-compounds (II) were cyclised to 2-thio-1-methylxanthines (III; R = H, Me, Ph, and CH_2Ph;

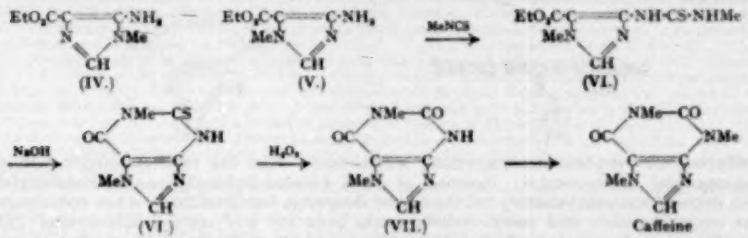


X = S). The 1-methylxanthines (III; R = Me and Ph; X = O) were obtained by a similar route, using methyl *iso*cyanate in the place of methyl *iso*thiocyanate. The present paper describes the extension of this work to include some natural purines and further homologues thereof.

Attention was first directed to the synthesis of 1-methylxanthine (III; R = H, X = O) which, although itself of no known outstanding importance, is of interest as an intermediate in the synthesis of caffeine. Ethyl 4-aminoglyoxaline-5-carboxylate (I; R = H) afforded ethyl 4-*N'*-methylureidoglyoxaline-5-carboxylate (II; R = H, X = O) on treatment with excess of methyl *iso*cyanate in warm pyridine. The ureido-compound readily dissolved in aqueous sodium hydroxide and acidification of the solution resulted in the precipitation of 1-methylxanthine, but the yield was low (50%), the alkaline filtrate containing some diazotisable base. It appears, therefore, that alkali caused partial reversion of the 4-*N'*-methylureido-compound to an aminoglyoxaline; no such decomposition was observed in the related cyclisation of the 4-*N'*-methylthioureido-analogue described in the earlier paper. Apart from analytical evidence and the murexide reaction, the formulation of the product as 1-methylxanthine was confirmed by methylation to caffeine by methyl sulphate (cf. Englemann, *Ber.*, 1909, **42**, 177).

The synthesis of a dimethylxanthine, either paraxanthine or 1 : 9-dimethylxanthine, required preliminary methylation of the glyoxaline ring of (I). Pyman and his co-workers, after an extensive study of the methylation of substituted glyoxalines, concluded that an electron-attracting substituent at $C_{(4)}$ favours the formation of 1- rather than of 3-methyl derivatives, whereas electron-donating groups act in the opposite manner (*J.*, 1910, 1814; 1922, 2616; 1924, 1431; 1925, 577). That more than this mere inductive effect of a 4(5)-substituent was concerned was shown by the more complicated example (Gulland and Story, *J.*, 1942, 232) of the methylation of methyl 4-nitroglyoxaline-5-carboxylate to methyl 4-nitro-1-methylglyoxaline-5-carboxylate despite the fact that of the 4- and the 5-substituent the latter was the less

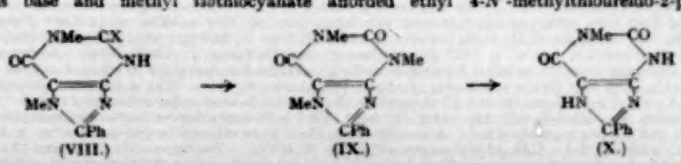
electropositive. No work was done on the methylation of aminoglyoxalines, mainly because of the difficulty of access of these compounds at that time so that it was of some additional interest to see how (I) behaved. With diazomethane, which had been successfully employed by Forsythe and Pyman (*J.*, 1925, 573) for the methylation of several glyoxalines, (I) yielded a diazotisable monomethyl derivative, necessarily therefore ethyl 4-amino-1-methylglyoxaline-5-carboxylate (V) or 5-amino-1-methylglyoxaline-4-carboxylate (IV). Of these two, one was known as the hydrochloride (Mann and Porter, *J.*, 1945, 751), and the other as the hydrochloride and free base (Cook, Downer, and Heilbron, *J.*, 1948, 2028). The product under discussion was the hitherto unknown 4-amino-compound (V). The methylation of the imino-group adjacent to the carbethoxy-substituent might be correlated with the obvious structural analogy between (I) and xanthine which is methylated in the 7- rather than the 9-position. The structure of the diazomethane methylation product was indeed confirmed by its conversion into caffeine: reaction of the methylated glyoxaline with methyl *iso*thiocyanate in boiling pyridine yielded 4-*N'*-methylthioureido-5-carbethoxyglyoxaline, dissolution of which in hot aqueous sodium hydroxide yielded a sparingly soluble sodium salt whence acid precipitated



2-thio-1 : 7-dimethylxanthine (VI); paraxanthine (VII) was obtained by treating the thiopurine in alkali with hydrogen peroxide, and converted into caffeine by methylation. This synthesis, apart from establishing beyond all doubt the structure of the monomethylation product, also proved to be a more satisfactory route to caffeine than the previous synthesis using 1-methylxanthine as an intermediate, although involving more stages.

The preparation of paraxanthine and caffeine derivatives containing hydrocarbon substituents situated at $C_{(8)}$ has not been extensively studied despite the pharmaceutical importance of caffeine. 8-Methyl- and 8-ethyl-caffeine have been prepared by treatment of the corresponding 8-alkyl ethers of caffeine with acetic anhydride (Huston and Allen, *J. Amer. Chem. Soc.*, 1934, **56**, 1793). This method, which is essentially an application of the preparation of 8-methylxanthines by reaction of uric acid and acetic anhydride (Boehringer and Son, *Chem. Zentr.*, 1901, II, 71; Golovchinskaya, *Chem. Abs.*, 1948, **42**, 2580), is very limited in scope and cannot, for example, be extended to include the syntheses of 8-propyl- and 8-butyl-caffeine. 8-Methyl-1 : 7-diethylxanthine (Mann and Porter, *loc. cit.*) is possibly the nearest approach to an 8-alkylparaxanthine recorded in the literature. Thus no general method has been established for the preparation of both alkyl- and aryl-caffeines and -paraxanthines, but as ethyl 4-amino-2-alkyl- and -aryl-glyoxaline-5-carboxylates were readily available from ethyl aminocyanoacetate they appeared to offer a useful route.

Ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (I; R = Ph) and diazomethane yielded a diazotisable monomethyl base, formulated, by analogy, as ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate and characterised as its 4-azo-2-naphthol derivative and picrate. This base and methyl *iso*thiocyanate afforded ethyl 4-*N'*-methylthioureido-2-phenyl-1-

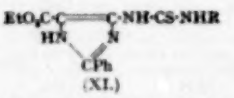


methylglyoxaline-5-carboxylate from which the sparingly soluble sodium salt of 2-thio-8-phenyl-1 : 7-dimethylxanthine was obtained in the usual way; the free xanthine (VIII; X = S)

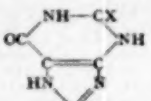
separated on acidification of the sodium salt. 8-Phenyl-1 : 7-dimethylxanthine (VIII; X = O), obtained by keeping the thiopurine in alkali with hydrogen peroxide, yielded 8-phenylcaffeine (IX) on methylation. 8-Phenylcaffeine was obtained in better overall yield from ethyl 4-amino-2-phenylglyoxaline-5-carboxylate, by the methylation of 8-phenyl-1-methylxanthine (X).

Ethyl 4-amino-2-benzyl-1-methylglyoxaline-5-carboxylate, obtained by reaction of ethyl 4-amino-2-benzylglyoxaline-5-carboxylate with diazomethane or methyl sulphate, afforded the 4-*N'*-methylthioureido-ester, 2-thio-8-benzyl-1 : 7-dimethylxanthine, 8-benzyl-1 : 7-dimethylxanthine, and, finally, 8-benzylcaffeine, by a similar route.

The use of urea in the place of the lachrymatory *iso*cyanates for the formation of the pyrimidine ring seemed to present a more economical synthesis of purines from aminoglyoxalines. The results, however, proved disappointing since not only was the condensation of urea and ethyl 4-amino-2-phenyl- and -2-benzyl-glyoxaline-5-carboxylate difficult to effect, but also much decomposition occurred on treatment with alkali and the yields of 8-phenyl- (XII; R = Ph, X = O) and 8-benzyl-xanthine (XII; R = CH_2Ph, X = O) were low. Urea reacted more smoothly with ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate, and 8-phenyl-7-



(XI.)



(XII.)

methylxanthine (8-phenylheteroxanthine) was obtained from the resultant ureide without accompanying decomposition. Reaction of ethyl 4-amino-2-phenylglyoxaline-5-carboxylate with thiourea was unsatisfactory but the desired thiopurine was obtained by a less direct route. The aminoglyoxaline and acetyl *iso*thiocyanate gave the 4-*N'*-acetylthioureido-ester (XI; R = Ac) which in hot concentrated hydrochloric acid afforded ethyl 4-thioureido-2-phenylglyoxaline-5-carboxylate (XI; R = H). Cyclisation of the last gave 2-thio-8-phenylxanthine (XII; R = Ph, X = S).

Experimental.

All the ethyl 4-amino-1-methylglyoxaline-5-carboxylates described below were diazotised in dilute hydrochloric acid and the resulting solutions, when poured into β-naphthol in aqueous sodium hydroxide, yielded red alkali-insoluble azo-dyes. The xanthines and 2-thioxanthines gave strong murexide reactions on oxidation with nitric acid, and potassium chlorate in hydrochloric acid, respectively.

Preparation of Caffeine.—(*a*) Ethyl 4-aminoglyoxaline-5-carboxylate (4·4 g.) in dry pyridine (8 c.c.) was warmed with methyl *iso*cyanate (2 c.c.) for 10 minutes. The solution was cooled, a further quantity of methyl *iso*cyanate (2 c.c.) added, and the solution again warmed; this procedure was repeated twice more. On being kept at 0°, *ethyl* 4-*N'-methylureidoglyoxaline-5-carboxylate* (4·0 g.) separated and crystallised from ethanol as needles, m. p. 147° (Found: C, 45·4; H, 5·8; N, 26·3. $C_8H_{12}O_3N_4$ requires C, 45·3; H, 5·7; N, 26·4%). The ureido-compound was dissolved in 5% aqueous sodium hydroxide (10 c.c.), and the solution heated at 80° for 20 minutes. On neutralisation of the solution with glacial acetic acid, 1-methylxanthine (0·3 g.) separated as a bluish salt-like solid. The filtrate was treated with sodium nitrite at 0° and poured into excess of alkaline β-naphthol; a red alkali-soluble azo-dye developed, indicating the presence of some aminoglyoxaline. 1-Methylxanthine was obtained as a pale blue microcrystalline solid by repeated acidification of its solution in alkali (Found: C, 43·2; H, 3·4. Calc. for $C_6H_6O_2N_4$: C, 43·4; H, 3·6%). Caffeine was obtained by methylation of 1-methylxanthine with methyl sulphate (cf. Englemann, *Ber.*, 1909, **42**, 177) and its identity confirmed by a mixed melting point with an authentic specimen.

(*b*) Diazomethane (2·8 g.) in ether (100 c.c.) was added to ethyl 4-aminoglyoxaline-5-carboxylate (2·1 g.) in methanol (40 c.c.); a steady evolution of nitrogen occurred for *ca.* 3 hours. The solution was concentrated *in vacuo* (to 40 c.c.) and the crystalline solid which separated at 0° was collected. More solid (0·8 g.) was precipitated on addition of cold light petroleum (b. p. 40—60°) to the filtrate. *Ethyl 4-amino-1-methylglyoxaline-5-carboxylate* was readily soluble in most common organic solvents; it was crystallised best from water or benzene–light petroleum, forming long needles, m. p. 140° (Found: C, 49·5; H, 6·6; N, 24·9. $C_7H_{11}O_2N_3$ requires C, 49·2; H, 6·4; N, 24·9%); ethyl 4-amino-3-methylglyoxaline-5-carboxylate has m. p. 192° (Cook, Downer, and Heilbron, *J.*, 1948, 2028). Addition of ethanolic hydrogen chloride to ethyl 4-amino-1-methylglyoxaline-5-carboxylate in ethanol yielded the hydrochloride, m. p. 195° (Mann and Porter, *J.*, 1945, 751, give m. p. 190°). The methylated glyoxaline (0·7 g.) and methyl *iso*thiocyanate (0·5 g.) in pyridine (2 c.c.) were heated under reflux for 2 hours. The cooled solution was diluted with ice water (10 c.c.), *ethyl* 4-*N'-methylthioureido*-1-*methylglyoxaline-5-carboxylate* (0·8 g.) being precipitated. A sample crystallised from ethanol as fine needles, m. p. 136° (Found: C, 45·0; H, 5·6. $C_9H_{14}O_2N_4S$ requires C, 44·6; H, 5·8%). The thioureido-compound (0·5 g.) readily dissolved in hot 5% aqueous sodium hydroxide and on slight cooling the sodium salt of 2-thio-1 : 7-dimethylxanthine separated as a mass of colourless threads, m. p. >360°. Addition of excess of glacial acetic acid to the sodium salt suspended in hot water yielded *2-thio*-1 : 7-*dimethylxanthine* as

clusters of laths, m. p. 355° (Found: C, 42·8; H, 4·1. $C_7H_8ON_4S$ requires C, 42·9; H, 4·1%). Conversion of ethyl 4-amino-1-methylglyoxaline-5-carboxylate into 2-thio-1 : 7-dimethylxanthine was accomplished in overall yield of 78% when the intermediate thioureido-compound was not recrystallised but dissolved in hot alkali and the solution acidified with glacial acetic acid.

Hydrogen peroxide (80 vol.; 5 c.c.) was added, with stirring, to a suspension of 2-thio-1 : 7-dimethylxanthine (0·9 g.) (as the sodium salt) in sodium hydroxide solution (5%; 25 c.c.). The sodium salt dissolved and, after 1 hour, the clear solution was heated at 80° until effervescence ceased. On acidification of the cooled solution with glacial acetic acid and storage at 0°, paraxanthine (0·7 g.) separated. The purine crystallised from water as needles, m. p. 299° (Found: C, 47·0; H, 4·4; N, 31·1. Calc. for $C_7H_8O_2N_4$: C, 46·7; H, 4·4; N, 31·1%). Finely powdered paraxanthine (0·21 g.) was added to ethereal diazomethane (0·4 g. in 20 c.c.); a brisk evolution of nitrogen ensued which ceased after 2 hours. The caffeine (0·18 g.) was collected and had m. p. 235°, undepressed on admixture with an authentic specimen.

Methylation of Ethyl 4-Amino-2-phenylglyoxaline-5-carboxylate.—Ethereal diazomethane (3·6 g. in 200 c.c.) was added to a suspension of finely powdered ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (10 g.) in methanol (20 c.c.); nitrogen was slowly evolved and the glyoxaline dissolved. After 24 hours some undissolved glyoxaline (1 g.) was filtered off and the filtrate evaporated *in vacuo*, leaving a gum which solidified on trituration under a mixture of light petroleum (b. p. 40—60°; 50 c.c.) and ethanol (5 c.c.). The yellow solid (6·7 g.), *ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate*, was readily soluble in cold acetone, ethanol, or warm chloroform, benzene, or ethyl acetate, soluble in warm water, and insoluble in light petroleum; a sample crystallised from benzene–light petroleum as large colourless needles, m. p. 141° (Found: C, 63·5; H, 6·3; N, 17·1. $C_{13}H_{15}O_2N_3$ requires C, 63·7; H, 6·1; N, 17·1%). The *picrate*, prepared in ethanol, crystallised from this solvent as yellow needles, m. p. 157° (Found: N, 17·8. $C_{19}H_{18}O_9N_6$ requires N, 17·7%). Ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate (0·5 g.) in 2*N*-hydrochloric acid (8 c.c.) was diluted with an equal volume of water and cooled to 0°. Sodium nitrite (0·2 g.) in water (3 c.c.) was dripped into the acid solution at >5°. The diazotised solution was poured into a cold solution of β-naphthol (0·5 g.) in 5% sodium hydroxide (20 c.c.); *ethyl 4-(2′-hydroxynaphthalene-1′-azo)-2-phenyl-1-methylglyoxaline-5-carboxylate* (0·4 g.) separated and was crystallised from glacial acetic acid as deep-red laths, m. p. 202—203° (Found: N, 14·5. $C_{23}H_{20}O_3N_5$ requires N, 14·0%).

A solution of ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate (3 g.) and methyl *iso*thiocyanate (3 g.) in pyridine (5 c.c.) was heated under reflux for 2 hours. The cooled pyridine solution was diluted with water (20 c.c.) whereupon *ethyl 4-N′-methylthioureido-2-phenyl-1-methylglyoxaline-5-carboxylate* (4·1 g.) was precipitated; this crystallised from ethyl acetate as needles, m. p. 191° (Found: N, 17·3. $C_{15}H_{19}O_2N_5S$ requires N, 17·6%). The thioureido-compound (3·4 g.) rapidly dissolved in hot 5% sodium hydroxide solution (30 c.c.) and on slight cooling the *sodium* salt of 2-thio-8-phenyl-1 : 7-dimethylxanthine separated as a mass of threads. A sample of the salt crystallised from a large volume of hot water as threads melting indefinitely above 360° (Found: N, 18·5. $C_{13}H_{11}ON_4SNa$ requires N, 19·0%). Glacial acetic acid was added to the above suspension of the sodium salt, whereby *2-thio-8-phenyl-1 : 7-dimethylxanthine* was precipitated as a gelatinous solid, m. p. 342° (Found: C, 57·0; H, 4·2; N, 20·9. $C_{13}H_{11}ON_4S$ requires C, 57·3; H, 4·4; N, 20·6%). The thiopurine (2·4 g.) was added to 5% sodium hydroxide (30 c.c.), and the solution, from which some of the sodium salt had separated, was stirred whilst 80-vol. hydrogen peroxide (10 c.c.) was added. The reaction was exothermic and when all the sodium salt had re-dissolved the solution was heated to 80° and acidified with acetic acid; *8-phenyl-1 : 7-dimethylxanthine* separated as very small plates, m. p. 326° (Found: C, 60·5; H, 5·0; N, 21·8. $C_{13}H_{12}O_2N_4$ requires C, 60·9; H, 4·7; N, 21·9%).

8-Phenylcaffeine.—(*a*) A solution of 8-phenyl-1 : 7-dimethylxanthine (0·7 g.) in sodium hydroxide solution (5%; 10 c.c.) was shaken with methyl sulphate (1·0 c.c.), and the precipitated solid (0·7 g.) collected. *8-Phenylcaffeine* crystallised from ethanol as needles, m. p. 187° (Found: C, 62·5; H, 5·2; N, 21·0. $C_{14}H_{14}O_2N_4$ requires C, 62·2; H, 5·1; N, 20·7%). (*b*) 8-Phenyl-1-methylxanthine (1 g.) (*J.*, 1949, 1071) in 5% sodium hydroxide (10 c.c.) was shaken with methyl sulphate (2·0 c.c.). On cooling of the clear solution to 0°, 8-phenylcaffeine (0·9 g.) separated, identical with the compound prepared as above.

Methylation of Ethyl 4-Amino-2-benzylglyoxaline-5-carboxylate.—(*a*) Ethereal diazomethane (2 g. in 80 c.c.) was added to ethyl 4-amino-2-benzylglyoxaline-5-carboxylate (5 g.) in methanol (100 c.c.). After 24 hours the solution was evaporated *in vacuo* and the yellow residue (5·10 g.) crystallised from ethanol, *ethyl 4-amino-2-benzyl-1-methylglyoxaline-5-carboxylate* being obtained as clusters of needles, m. p. 155° (Found: C, 64·5; H, 6·3; N, 16·6. $C_{14}H_{17}O_2N_3$ requires C, 64·9; H, 6·7; N, 16·2%). The glyoxaline was readily soluble in cold chloroform, soluble in warm ethyl acetate or benzene, and insoluble in water or ether.

(*b*) Ethyl 4-amino-2-benzylglyoxaline-5-carboxylate (0·5 g.), dissolved in the minimum quantity of dilute hydrochloric acid, was poured into 5% sodium hydroxide (20 c.c.) at 60° with stirring. The clear solution was rapidly cooled and shaken mechanically with methyl sulphate (0·4 c.c.) for 5 minutes; the 1-methylglyoxaline (0·4 g.) separated as a granular solid, m. p. 146°. After crystallisation from ethanol the compound proved to be identical with the former product.

(*c*) Shaking an alkaline solution of ethyl 4-amino-2-benzylglyoxaline-5-carboxylate (0·5 g.) with methyl iodide (0·3 g.) for 12 hours gave the same methylated glyoxaline (0·38 g.) in an impure state.

8-Benzylcaffeine.—Ethyl 4-amino-2-benzyl-1-methylglyoxaline-5-carboxylate (2·5 g.) and methyl *iso*thiocyanate (2·0 g.) were heated in pyridine (2 c.c.) under reflux for 2 hours. On dilution of the cooled pyridine solution with water, *ethyl 4-N′-methylthioureido-2-benzyl-1-methylglyoxaline-5-carboxylate* (3·2 g.) separated. This was readily soluble in cold chloroform or warm benzene, soluble in ethanol, acetic acid, or hot ethyl acetate; a sample crystallised from ethanol as hexagonal prisms, m. p. 124° (Found: C, 47·5; H, 6·0; N, 16·7. $C_{16}H_{20}O_2N_5S$ requires C, 47·8; H, 6·0; N, 16·9%). On alkali treatment of the thioureido-compound (2 g.) in the usual way, followed by acidification, *2-thio-8-benzyl-1 : 7-dimethylxanthine* (1·6 g.) was obtained as small needles, m. p. 295° (Found: C, 58·9; H, 4·9; N, 19·6.

$C_{18}H_{14}ON_4S$ requires C, 58·7; H, 4·9; N, 19·6%). 80-Vol. hydrogen peroxide (7 c.c.) was added to 2-thio-9-benzyl-1 : 7-dimethylxanthine (1 g.) in 5% sodium hydroxide (15 c.c.); heat was evolved and the solution was set aside until all the solid had dissolved. On acidification of the solution at 80°, *8-benzyl-1 : 7-dimethylxanthine* (0·8 g.) was obtained as small needles, m. p. 252° (Found: C, 62·2; H, 5·3; N, 21·1. $C_{14}H_{14}O_2N_4$ requires C, 62·2; H, 5·2; N, 20·7%). The xanthine (0·6 g.) was suspended in ethereal diazomethane (0·6 g. in 25 c.c.) and when no more nitrogen was evolved (*ca.* 2 hours) the crystalline solid (0·4 g.) was filtered off. More solid (0·15 g.) was obtained on evaporation of the filtrate (to 5 c.c.) and cooling to 0°. *8-Benzylcaffeine* was soluble in acid, but insoluble in alkali, and crystallised from ethanol as rods, m. p. 161—163° (Found: C, 64·2; H, 5·9; N, 19·5. $C_{15}H_{16}O_2N_4$ requires C, 63·7; H, 5·6; N, 19·7%).

8-Phenylxanthine.—Ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (1·5 g.) and urea (0·7 g.) were heated in pyridine under reflux for 1½ hours; ammonia was evolved, and the solution became discoloured. The solution was diluted with ice-water (50 c.c.) whereby an oil was precipitated, which solidified slowly. The fawn-coloured solid (1·4 g.) was crystallised from aqueous ethanol, dissolved in 5% sodium hydroxide solution (20 c.c.), and heated to 80°; the solution became red and on acidification with excess of acetic acid a dark gummy solid separated which redissolved on rapid stirring and separated again on cooling as an amorphous red solid (0·3 g.). *8-Phenylxanthine* was dissolved in 2% sodium hydroxide (10 c.c.) (charcoal), and precipitated with acid. This was repeated until the purine was obtained as a pale red gelatinous solid melting indefinitely at *ca.* 360° (decomp.) (Found: C, 57·5; H, 3·9; N, 24·7. $C_{11}H_8O_2N_4$ requires C, 57·9; H, 3·5; N, 24·5%).

8-Benzylxanthine.—Ethyl 4-amino-2-benzylglyoxaline-5-carboxylate (2 g.) and urea (0·7 g.) were heated in pyridine (4 c.c.) under reflux for 4 hours. The solution was cooled and diluted with ice-water (100 c.c.); the precipitated oil solidified on stirring at 0—5°. A solution of the solid in 5% sodium hydroxide (20 c.c.) was heated to 80°. On acidification of the hot somewhat discoloured solution with glacial acetic acid a dark solid was precipitated which redissolved on rapid stirring; *8-benzylxanthine* (0·4 g.) separated as a red solid on cooling. After repeated acidification of its solution in alkali, the xanthine was obtained as a reddish gelatinous solid which darkened and softened above 300° (Found: N, 23·5. $C_{12}H_{10}O_2N_4$ requires N, 23·1%).

8-Phenyl-7-methylxanthine.—Ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate (1 g.) and urea (0·5 g.) were heated in pyridine (2 c.c.) under reflux for 3 hours; ammonia was evolved and, when the solution was kept at 0°, solid (0·2 g.), m. p. 193—194°, separated. More of the 4-ureido-derivative (0·3 g.) was obtained on dilution of the mother-liquor with water (20 c.c.). The ureide was dissolved in hot 5% sodium hydroxide (15 c.c.) and acidified; *8-phenyl-7-methylxanthine* separated as colourless prisms, m. p. 340° (Found: N, 23·2. $C_{12}H_{10}O_2N_4$ requires N, 23·1%).

2-Thio-8-phenylxanthine.—Ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (2·2 g.) and acetyl isothiocyanate (1·5 g.) were heated in chloroform (80 c.c.) under reflux for 45 minutes. The glyoxaline rapidly dissolved and yellow crystals (1·4 g.) separated. More solid (1·3 g.) separated on evaporation of the solvent *in vacuo*. *Ethyl 4-N'-acetylthioureido-2-phenylglyoxaline-5-carboxylate* crystallised from methanol as octahedra, m. p. 225° (Found: C, 54·1; H, 4·8. $C_{15}H_{16}O_3N_4S$ requires C, 54·2; H, 4·8%). The acetylthioureido-compound (0·7 g.) was suspended in 2*N*-hydrochloric acid (20 c.c.) containing ethanol (10 c.c.), and the solution heated under reflux for one hour. *Ethyl 4-thioureido-2-phenylglyoxaline-5-carboxylate* (0·5 g.) separated on cooling of the solution; a sample crystallised from ethanol as rods, m. p. 256° (Found: C, 53·4; H, 4·9; N, 19·3. $C_{13}H_{14}O_2N_4S$ requires C, 53·8; H, 4·8; N, 19·3%). Dissolution of this ester in alkali, and subsequent acidification of the hot solution, yielded *2-thio-8-phenylxanthine* as a colourless gelatinous solid (Found: C, 54·3; H, 3·6. $C_{11}H_8ON_4S$ requires C, 54·1; H, 3·3%).

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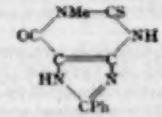
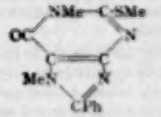
385. *Studies in the Azole Series. Part XXX. New Syntheses of 2- and 8-Aminopurines.*

By A. H. Cook and G. H. Thomas.

Attempts to synthesise guanine derivatives from ethyl 4-aminoglyoxaline-5-carboxylates are described; more obvious routes proved unsuccessful, but a ready synthesis of dimethylguanines was developed by cyclising 4-*N'*-methylthioureidoglyoxaline-5-carboxylates with methylamine in the presence of mercuric oxide. 8-Methylaminopurines have been obtained by treatment of 5-*N'*-methylthioureido-4-aminopyrimidines with mercuric oxide.

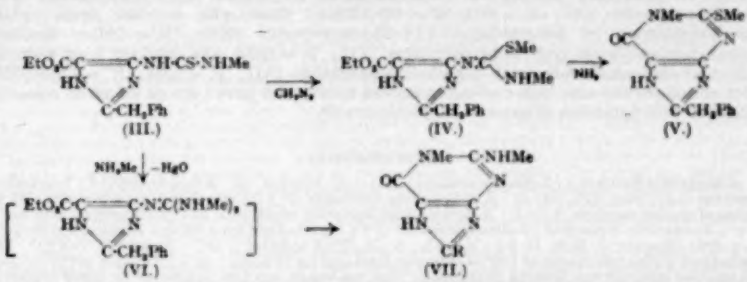
The extension of the syntheses of purines from azoles to include adenine and some of its derivatives has been described in an earlier paper in this series (Cook and Smith, Part XXIII, *J.*, 1949, 3001). The present contribution describes some attempts to synthesise derivatives of the second important class of aminopurines, guanines, from 4-aminoglyoxaline-5-carboxylates. Such an undertaking envisaged the preliminary formation of 4-guanidinoglyoxaline-5-carboxylates, from which the guanine derivatives might be obtained by cyclisation with

elimination of ethanol. The condensation of guanidine with the aminoglyoxalines seemed a likely route to such intermediates, but it was found that fusion of the two reactants resulted in

(I.)   (II.)

only sluggish elimination of ammonia, even at temperatures at which the glyoxaline decomposed. Similar difficulty was found with the salts of *S*-alkylthioureas. Obviously, then, a method had to be developed for synthesising the guanidinoglyoxalines under milder conditions.

Accordingly, attention was turned to the formation of the guanidino-portion of the purine by replacement of a methylthio-substituent with ammonia. 2-Thio-8-phenyl-1-methylxanthine (I) (Cook, Heilbron, Davis, and Thomas, Part XIV, *J.*, 1949, 1071) yielded 2-methylthio-8-phenyl-1 : 7-dimethylxanthine (II) on methylation with methyl sulphate in alkali, and the methylated compound was heated in ethanolic ammonia at 130° for 24 hours in an attempt to obtain 8-phenyl-1 : 7-dimethylguanine, but no methanethiol was eliminated and the purine was recovered unchanged. An obvious modification, therefore, was the use of an *S*-methyl*iso*thioureidoglyoxaline in the place of (I), since *S*-alkyl*iso*thioureas very readily react with ammonia yielding guanidines. Ethyl 4-*N'*-methylthioureido-2-benzylglyoxaline-5-carboxylate (III)

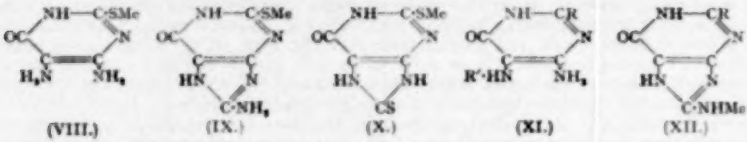


afforded ethyl 4-*N'S*-dimethyl*iso*thioureido-2-benzylglyoxaline-5-carboxylate (IV) on treatment with ethereal diazomethane. Here, again, the methylthio-group was not eliminated in ethanolic ammonia at 150° for 12 hours, 2-methylthio-8-benzyl-1-methylxanthine (V) being obtained. The stability of the methylthio-substituent may perhaps be correlated with the aromatic nature of the purine ring system, though in view of similar failures in the pyrimidine series, a complex of factors may well be responsible (see, for example, Andrews, Anand, Todd, and Topham, *J.*, 1949, 2491).

The method eventually adopted was facilitated by a recent observation that *N'*-alkyl-*N''*-*p*-chlorophenylguanidinopyrimidines could be obtained from the corresponding thioureas by treatment in ammoniacal solution with mercuric oxide, the thiol group being eliminated as the metal sulphide and replaced by an amino-group (Crowther, Curd, and Rose, *J.*, 1948, 587). It was thought that by applying the same type of reaction to the thioureido-compound (III), a guanidinoglyoxaline would result which would afford 8-benzyl-1-methylguanine on cyclisation. Unfortunately it was not possible to use ammonia in this reaction, since, like aqueous sodium hydroxide, it immediately cyclised the thioureido-compound to the ammonium salt of 2-thio-8-benzyl-1-methylxanthine (Part XIV, *loc. cit.*). Methylamine did not effect this rapid cyclisation and so, when ethyl 4-*N'*-methylthioureido-2-benzylglyoxaline-5-carboxylate and mercuric oxide were gently heated in aqueous methylamine, mercuric sulphide was precipitated and acidification of the mother-liquor yielded 8-benzyl-1 : N^2-dimethylguanine (VII; R = CH_2Ph) : cyclisation of the intermediate guanidinoglyoxaline (VI) evidently had occurred spontaneously. In a like manner, ethyl 4-*N'*-methylthioureido-glyoxaline- and -2-phenylglyoxaline-5-carboxylate afforded 1 : N^2-dimethyl- (VII; R = H) and 8-phenyl-1 : N^2-dimethyl-guanine (VII; R = Ph) respectively. These dimethylguanines gave a characteristic colour reaction under murexide conditions :

oxidation in concentrated hydrochloric acid with potassium chlorate, and evaporation to dryness left a strong mauve stain which changed to red on moistening with 10% aqueous sodium hydroxide. 1 : N^3-Dimethylguanine, like guanine itself (Traube, *Ber.*, 1900, **33**, 1378), left a glazed yellow residue on evaporation with nitric acid which changed to a red-violet stain when moistened with alkali.

The ability of mercuric oxide to remove hydrogen sulphide from a thioureido-compound has also provided a ready synthesis of 8-aminopurines. Johns and Baumann (*J. Biol. Chem.*, 1913, **14**, 387) found that, when 4 : 5-diamino-6-hydroxy-2-methylthiopyrimidine (VIII) was fused with thiourea, 8-amino-6-hydroxy-2-methylthiopurine (IX) was obtained instead of the expected 6-hydroxy-8-mercapto-2-methylthiopurine (X); this unique case was caused by decomposition of thiourea to guanidine *iso*thiocyanate before reaction occurred. The synthesis suggested a possible route to 8-aminopurines.



(VIII.) (IX.) (X.) (XI.) (XII.)

4 : 5-Diamino-2 : 6-dihydroxypyrimidine (XI; R = OH, R' = H) readily reacted with methyl *iso*thiocyanate yielding the hemihydrate of 4-amino-5-*N'*-methylthioureido-2 : 6-dihydroxypyrimidine (XI; R = OH, R' = CS·NHMe), which with mercuric oxide yielded the hemihydrate of 8-methylamino-2 : 6-dihydroxypurine (XII; R = OH). Similarly 8-methylamino-6-hydroxy-2-methylthiopurine (XII; R = SMe) was obtained from 4-amino-5-*N'*-methylthioureido-6-hydroxy-2-methylthiopyrimidine (XII; R = SMe; R' = CS·NHMe). Both amino-purines were high-melting crystalline solids which gave a strong murexide colour on oxidation with potassium chlorate in hydrochloric acid.

Experimental.

2-*Methylthio*-8-*phenyl*-1 : 7-*dimethylxanthine* (II).—A solution of 2-thio-8-phenyl-1 : 7-dimethylxanthine (2 g.) (Part XIV, *loc. cit.*) in 10% sodium hydroxide (10 c.c.) was shaken for 5 minutes with an excess of methyl sulphate (1 c.c.). A gummy solid separated which solidified on trituration with water at 0°; 2-*methylthio*-8-*phenyl*-1 : 7-*dimethylxanthine* (1·8 g.) crystallised from ethanol as colourless threads, m. p. 235° (Found: C, 58·7; H, 5·2; N, 19·2. $C_{14}H_{14}ON_4S$ requires C, 58·7; H, 4·9; N, 19·6%). The methylated purine was heated at 130° in ethanolic ammonia for 24 hours; on acidification of the solution the starting material was isolated unchanged. The compound was also unaffected by being heated in 2*N*-hydrochloric acid or 20% sodium hydroxide under reflux.

2-*Methylthio*-8-*benzyl*-1-*methylxanthine* (V).—A suspension of ethyl 4-*N'*-methylthioureido-2-benzylglyoxaline-5-carboxylate (2 g.) in methanol (5 c.c.) was treated with excess of ethereal diazomethane in portions until the yellow colour persisted after stirring; all the thioureido-compound had dissolved. On evaporation to 5 c.c. and storage at 0°, a colourless solid (1·3 g.) separated which was collected and washed with light petroleum (b. p. 40—60°; 5 c.c.). The filtrate and washings left a residual gum on evaporation *in vacuo*, which was taken up in ethanol (5 c.c.). More solid (0·3 g.) was precipitated on addition of light petroleum to the ethanol solution. *Ethyl* 4-*N'*-*S*-*dimethylisothioureido*-2-*benzylglyoxaline*-5-*carboxylate* was obtained as colourless prisms, m. p. 124—125°, on repeated crystallisation from ethanol (Found: C, 57·6; H, 5·9; N, 16·9. $C_{16}H_{20}O_2N_4S$ requires C, 57·8; H, 6·0; N, 17·2%). It (0·5 g.) was dissolved in ethanol (10 c.c.), liquid ammonia (3 c.c.) added, and the solution heated at 150° for 12 hours in a sealed tube; no methanethiol was detected and, on acidification of the alcohol solution, 2-*methylthio*-8-*benzyl*-1-*methylxanthine* (0·3 g.) was precipitated. The thiopurine was dissolved in hot pyridine and the solution diluted with hot water and cooled; it separated as small laths which softened at 290° and melted at *ca.* 340° (Found: C, 58·5; H, 4·6. $C_{14}H_{14}ON_4S$ requires C, 58·7; H, 4·9%). The purine gave the murexide reaction on oxidation with potassium chlorate in hydrochloric acid.

8-*Benzyl*-1 : N^3-*dimethylguanine* (VII; R = CH_2Ph).—Ethyl 4-*N'*-methylthioureido-2-benzylglyoxaline-5-carboxylate (2 g.) was dissolved in cold 5% aqueous methylamine (150 c.c.). Mercuric oxide (2 g.) was then added (the suspension began to darken even in the cold) and the solution was heated over a free flame with rapid swirling until the colour had changed from red to black. Mercuric sulphide was filtered off while the solution was still hot and washed with hot water (10 c.c.). The combined filtrate and washings were acidified with excess of glacial acetic acid with stirring; a gum was precipitated which solidified in the presence of excess of acid. The solid (1·7 g.) was readily soluble in cold 2*N*-sodium hydroxide or concentrated hydrochloric acid, soluble in warm dilute hydrochloric acid, and moderately soluble in hot water. The crude material (1·5 g.) was heated in ethanol (150 c.c.) under reflux, the greater part dissolving to leave 2-thio-8-phenyl-1-methylxanthine (0·15 g.). The ethanol solution was concentrated (to 30 c.c.) and cooled to 0°, 8-*benzyl*-1 : N^3-*dimethylguanine* (1·2 g.) separating. The guanine separated from ethanol as small crystals which darkened at 285° and had m. p. 315° (Found: C, 62·0; H, 5·7; N, 26·1. $C_{14}H_{15}ON_5$ requires C, 62·4; H, 5·6; N, 26·0%). Oxidation with potassium chlorate

in hydrochloric acid, and evaporation to dryness, left a strong mauve stain which changed to red when moistened with sodium hydroxide solution. The guanine was dissolved in a hot saturated solution of picric acid in methanol and the solution rapidly filtered; the *picrate* separated as yellow rods, m. p. 267° (decomp.) (Found: C, 48·4; H, 3·6. $C_{11}H_{11}O_9N_8$ requires C, 48·2; H, 3·6%).

8-Phenyl-1 : N^1-*dimethylguanine* (VII; R = Ph).—Ethyl 4-*N'*-methylthioureido-2-phenylglyoxaline-5-carboxylate (2 g.) and mercuric oxide (2 g.) were rapidly stirred together in 10% aqueous methylamine (150 c.c.) at 50°. After 15 minutes the colour of the suspended solid had changed from red to black; the temperature then was raised to 80° and the mercuric sulphide filtered off while the solution was still hot. When the solution was kept at 0°, long thin yellow threads of *8-phenyl*-1 : N^1-*dimethylguanine* (0·8 g.) separated. Neutralisation of the mother-liquor with glacial acetic acid yielded more of the guanine (0·4 g.). The purine was purified by precipitation with acetic acid from its solution in aqueous ammonia, being obtained as colourless threads, m. p. 360° (Found: C, 61·6; H, 5·0; N, 27·5. $C_{12}H_{11}ON_4$ requires C, 61·2; H, 5·1; N, 27·5%). It was insoluble in water and readily soluble in cold alkali or warm acid. Oxidation with potassium chlorate in concentrated hydrochloric acid, and evaporation to dryness, left a strong mauve stain which changed to red when moistened with sodium hydroxide solution.

1 : N^1-*Dimethylguanine* (VII; R = H).—A solution of ethyl 4-*N'*-methylthioureidoglyoxaline-5-carboxylate (1 g.) in 5% aqueous methylamine (100 c.c.) was heated with mercuric oxide (1 g.) over a free flame with rapid swirling until the suspended solid became black. Mercuric sulphide was filtered off and the filtrate acidified with acetic acid; on cooling, 1 : N^1-*dimethylguanine* separated. It was readily soluble in aqueous sodium hydroxide and could be obtained as needles, m. p. 345—350°, on neutralisation of the alkaline solution with acetic acid and storage at 0° (Found: C, 47·2; H, 5·3; N, 38·9. $C_7H_9ON_5$ requires C, 46·9; H, 5·0; N, 39·1%); it gave the murexide reaction with potassium chlorate in hydrochloric acid. 1 : N^1-Dimethylguanine, like guanine itself (Traube, *Ber.*, 1900, **33**, 1378), left a glazed yellow residue on evaporation of a solution in nitric acid, which changed to a red-violet stain when moistened with alkali.

8-Methylamino-2 : 6-dihydroxypurine (XII; R = OH).—4 : 5-Diamino-2 : 6-dihydroxypyrimidine was prepared from 4-amino-2 : 6-dihydroxypyrimidine by nitrosation (Blitz and Schmidt, *Annalen*, 1923, **431**, 94) and reduction of the 5-nitroso-compound so formed (Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667). 4 : 5-Diamino-2 : 6-dihydroxypyrimidine sulphate (9·6 g.) was dissolved in the minimum quantity of 5% sodium hydroxide and the solution warmed with methyl *iso*thiocyanate for 30 minutes. On acidification of the hot solution with glacial acetic acid, *4-amino-5-methylthioureido-2 : 6-dihydroxypyrimidine* (8·6 g.) separated. The pyrimidine was sparingly soluble in water and was purified by acidification of its solution in aqueous sodium hydroxide, being obtained as needles of the *hemihydrate* (Found: C, 32·0; H, 4·6; N, 31·2. $C_5H_7O_2N_5S,\frac{1}{2}H_2O$ requires C, 32·1; H, 4·5; N, 31·2%). The thioureido-compound (8 g.) was suspended in water (100 c.c.) and rapidly stirred with mercuric oxide (6 g.) at 50—60° until the colour had changed from red to black (*ca.* 30 minutes). Mercuric sulphide was filtered off while the solution was still hot, and, on cooling, the filtrate gave a lemon-yellow solid (0·5 g.). The mercuric sulphide was extracted with hot 5% sodium hydroxide; acidification of the alkaline extracts with acetic acid yielded more (4·5 g.) of the yellow precipitate. The purine was purified by acidification of its solution in aqueous ammonia, whereby it was obtained as *8-methylamino-2 : 6-dihydroxypurine hemihydrate* (Found: C, 37·6; H, 4·2. $C_6H_7O_2N_5,\frac{1}{2}H_2O$ requires C, 37·9; H, 4·2%). The purine melted indefinitely above 360° and gave a strong murexide reaction on oxidation with potassium chlorate in hydrochloric acid.

8-Methylamino-6-hydroxy-2-methylthiopurine (XII; R = SMe).—4 : 5-Diamino-6-hydroxy-2-methylthiopyrimidine (5 g.) was suspended in pyridine (100 c.c.) at 70°, and a solution of methyl *iso*thiocyanate (2·5 g.) in pyridine was added with stirring. The reaction was exothermic and the diaminopyrimidine rapidly dissolved giving, momentarily, a clear solution from which the pyrimidine (6 g.) separated. *4-Amino-5-N'-methylthioureido-6-hydroxy-2-methylthiopyrimidine hemihydrate*, crystallised from water as hexagonal plates and rods, m. p. 225—228° (Found: C, 33·0; H, 5·1; N, 27·4. $C_7H_{11}ON_5S_2,\frac{1}{2}H_2O$ requires C, 33·1; H, 4·7; N, 27·5%). The pyrimidine (4 g.) and mercuric oxide (4 g.) were rapidly stirred in water (50 c.c.) at 60° until the suspended solid was black. The hot solution was filtered, and the filtrate evaporated *in vacuo* until solid began to separate; on cooling, *8-methylamino-6-hydroxy-2-methylthiopurine monohydrate* separated as threads. It was purified by acidification of its solution in aqueous sodium hydroxide, separating as needles, m. p. 326° (Found: C, 36·5; H, 5·2; N, 30·2. $C_7H_9ON_5S,H_2O$ requires C, 36·7; H, 4·8; N, 30·6%); *ca.* 50% of the water of crystallisation was lost on drying at 12 mm. over boiling xylene for 12 hours (Found: C, 37·5; H, 4·9; N, 32·2. $C_7H_9ON_5S,\frac{1}{2}H_2O$ requires C, 38·2; H, 4·5; H, 31·8%). The purine gave a strong murexide colour on oxidation with potassium chlorate in hydrochloric acid.

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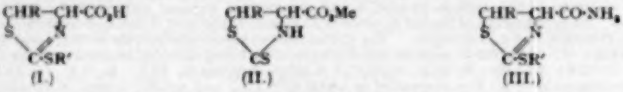
386. *Studies in the Azole Series. Part XXXI. The Interaction of Amines and 2-Mercapto-4-alkylidene- or -arylidene-5-thiazolinones.*

By A. H. Cook, G. D. Hunter, and J. R. A. Pollock.

Apart from certain exceptional cases, interaction of a 2-mercapto-alkylidene- or -arylidene-thiazolin-5-one and an amine gives a mixture of a thiazoline such as (III; R′ = H) and a 2-thiohydantoin (*e.g.*, XVII). The former products are converted into 5-substituted thiazolidine-4-carboxyamides (*e.g.*, IV; R′ = NH_2) from which the amides of substituted cysteines may be obtained.

The preparations of aminomercapto-acids from 2-mercaptothiazolines which were reported earlier in this series (*J.*, 1948, 1337, 1060; 1949, 1437, 3007; see also Cook, Heilbron, and Shaw, CPS, 311) involved the use of concentrated hydrochloric acid, with or without reducing agents. It was expected that certain of the reactions then envisaged would not succeed under these conditions, and the fission of 2-mercapto-5-*p*-methoxyphenylthiazoline-4-carboxylic acid (I; R = *p*-MeO·C_6H_4, R′ = H) (Cook, Harris, Pollock, and Swan, *J.*, in the press) proved to be of this kind.

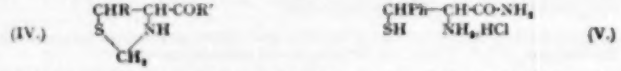
The observation (Bentley, Catch, Cook, Heilbron, and Shaw, CPS, 267) that Δ^2-thiazolines can be reduced to thiazolidines by amalgamated aluminium offered, however, a possible alternative approach. Exploratory attempts to reduce the methyl ester of (I; R = *p*-MeO·C_6H_4; R′ = H) in this way were unsuccessful, possibly because of the tendency of such compounds to behave as the corresponding thiones (II), rather than as thiazolines. Methylation of the methyl ester which was expected to yield a true thiazoline gave oils of doubtful purity, and



(I.) (II.) (III.)

attention was therefore directed to amides such as (III), which were expected to provide crystalline intermediates and to be of interest *per se* in leading to the hitherto unobtained amides of cysteine derivatives and thence of penicillins; the potential importance of the last series was recently demonstrated when benzylpenicillinamide was obtained from the antibiotic itself (Carpenter, *J. Amer. Chem. Soc.*, 1948, **70**, 2964).

When α-2-methylthio-5-phenylthiazoline-4-carboxyamide (III; R = Ph, R′ = Me), obtained by the reaction of (VI; R = Ph, R′ = H) with ammonia followed by methylation, was treated with amalgamated aluminium, methanethiol was evolved, and 5-phenylthiazolidine-4-carboxyamide (IV; R = Ph, R′ = NH_2) was produced. Thiazolidines of this type are dissociated in varying degrees into the constituent amino-mercaptans and formaldehyde in solution. Thus Ratner and Clark (*ibid.*, 1937, **59**, 200) showed that treatment of thiazolidine-4-carboxylic acid (IV; R = H, R′ = OH) with benzyl chloride or mercuric chloride gave good yields of cysteine derivatives, though distillation of solutions of the thiazolidine in dilute hydrochloric acid removed formaldehyde only slowly. Similarly, with (IV; R = Ph, R′ = NH_2) no formaldehyde could be detected in the distillate from dilute hydrochloric acid solution, but the mercaptide precipitated by mercuric chloride gave a good yield of 1-amino-2-mercapto-2-phenylpropionamide hydrochloride (V).

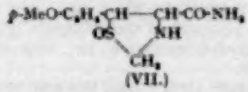


(IV.) (V.)

2-Mercapto-4-*p*-methoxybenzylidene-5-thiazolinone (VI; R = *p*-MeO·C_6H_4, R′ = H) and ammonia gave a mixture from which the two diastereoisomerides of 2-mercapto-5-*p*-methoxyphenylthiazoline-4-carboxyamide (III; R = *p*-MeO·C_6H_4, R′ = H) were isolated. One of these was reduced, through its 2-methylthio-derivative (III; R = *p*-MeO·C_6H_4, R′ = Me), to 5-*p*-methoxyphenylthiazolidine-4-carboxyamide (IV; R = *p*-MeO·C_6H_4, R′ = NH_2). An attempt to convert the latter product into the corresponding carboxylic acid by means of nitrous acid gave a neutral product which contained one oxygen atom more than the parent compound and was tentatively formulated as the *S*-oxide (VII). The acid (IV; R = *p*-MeO·C_6H_4, R′ = OH) was subsequently obtained from the acid (I; R = *p*-MeO·C_6H_4, R′ = H) (Cook, Harris, Pollock, and Swan, *loc. cit.*).

A preparation of 2-mercapto-5-*p*-hydroxyphenylthiazoline-4-carboxylic acid (I; R = *p*-HO·C$_6$H$_4$, R′ = H) has already been reported (*idem*, *ibid.*) and an alternative route to this compound was derived from the interaction of 2-mercapto-4-*p*-acetoxybenzylidene-5-thiazolinone (VI; R = *p*-AcO·C$_6$H$_4$, R′ = H) with ammonia. This reaction was, however, distinguished from others between similar compounds by the elimination of hydrogen sulphide, two products being obtained: one of these, 2-thio-5-*p*-hydroxybenzylidenehydantoin (VIII; R = *p*-HO·C$_6$H$_4$), was also prepared (*a*) from ammonia and 2-methylthio-4-*p*-acetoxybenzylidene-5-thiazolinone (VI; R = *p*-AcO·C$_6$H$_4$, R′ = Me), and (*b*) from ammonia and an acetyl derivative prepared from *p*-hydroxybenzaldehyde, potassium thiocyanate, and acetic anhydride; the remainder of the reaction product appeared to be a mixture, from which one of the diastereoisomeric forms of 2-mercapto-5-*p*-hydroxyphenyl-2-thiazoline-4-carboxyamide (III; R = *p*-HO·C$_6$H$_4$, R′ = H) was isolated. The crude mixture with sodium hydroxide gave ammonia and the corresponding acid, identical with material prepared otherwise (Cook, Harris, Pollock, and Swan, *loc. cit.*).

(VI.)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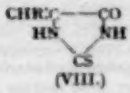
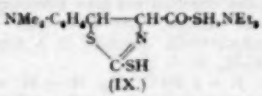

(VIII.)

The formation of 2-thiohydantoins as above from 2-mercapto-5-thiazolinones parallels their occurrence as the sole reaction products of amines with 2-benzylthio-5-thiazolinones (Cook, Harris, Heilbron, and Shaw, *loc. cit.*), and is now, indeed, known to be not unusual with such mercapto-compounds. Thus 2-mercapto-4-(2-furfurylidene)-5-thiazolinone (VI; R = C$_4$H$_3$O, R′ = H) with ammonia gave a mixture of 2-thio-5-(2-furfurylidene)hydantoin (VIII; R = C$_4$H$_3$O) with 2-mercapto-5-(2-furyl)thiazoline-4-carboxyamide (III; R = C$_4$H$_3$O, R′ = H). The thiohydantoin was characterized as its 2-methylthio-derivative and identified by comparison with specimens prepared (*a*) by the reaction of furfuraldehyde, potassium thiocyanate, and acetic anhydride, and (*b*) by treating 2-methylthio-4-(2-furfurylidene)-5-thiazolinone (VI; R = C$_4$H$_3$O, R′ = Me) with ammonia. Only one diastereoisomeride of the amide (III; R = C$_4$H$_3$O, R′ = H) appeared to be present, and this was characterized as its 2-methylthio-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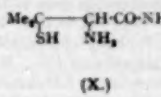
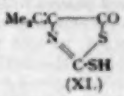
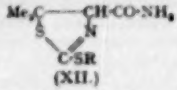

(X.)


(XI.)

derivative, which was reduced to 5-(2-furyl)thiazolidine-4-carboxyamide (IV; R = C$_4$H$_3$O, R′ = NH$_2$). Neither the furfurylidenethiazolinone nor 2-mercapto-4-*p*-nitrobenzylidene-5-thiazolinone (VI; R = *p*-NO$_2$·C$_6$H$_4$, R′ = H) gave satisfactory products under the now familiar ring-turning conditions in the presence of sodium methoxide or sodium hydroxide, and pure material was not isolated by treatment of the thiazolinones in alcoholic triethylamine with hydrogen sulphide. The *p*-nitrobenzylidenethiazolinone, which was characterized as its 2-methylthio-derivative, reacted with ammonia to yield a thiohydantoin exclusively, but the hydrogen sulphide liberated in the reaction appeared to cause reduction of the nitro-group; the major product, however, remains unidentified as, despite analytical indications, its properties did not agree with those of 5-*p*-aminobenzylidene-2-thiohydantoin given by Namjoshi and Dutt (*J. Indian Chem. Soc.*, 1931, **8**, 241). 2-Mercapto-4-*p*-dimethylaminobenzylidene-5-thiazolinone (VI; R = *p*-NMe$_2$·C$_6$H$_4$, R′ = H) yielded the corresponding thiohydantoin (VIII; R = *p*-NMe$_2$·C$_6$H$_4$) in ammonia, but on treatment with hydrogen sulphide in methanolic triethylamine it gave triethylammonium 2-mercapto-5-*p*-dimethylaminophenylthiazoline-4-thiolcarboxylate (IX). As the first step in the attempted synthesis of penicillamine amide (X), 2-mercapto-4-*iso*propylidene-5-thiazolinone (XI) was treated with ammonia, giving 2-mercapto-5 : 5-dimethylthiazoline-4-carboxyamide (XII; R = H) and thence the methylthio-derivative (XII; R = Me). The last compound was remarkable in yielding a small quantity only of methanethiol on reduction with amalgamated aluminium, and the main product was isomeric with the starting material. Its crystalline form, solubility and melting point were different, and it is tentatively formulated as 2-thio-3 : 5 : 5-trimethylthiazolidone-4-carboxyamide (XIII). Attempts to reduce (XII; R = H) directly to the thiazolidine with amalgamated aluminium or magnesium and sulphur dioxide were abortive. In attempts to prepare compounds similar to the thiazoline (XII; R = H), the thiazolinone (XI) was treated

with dimethylamine: a novel reaction occurred, leading to a basic compound, 2-dimethylamino-5 : 5-dimethylthiazoline-4-carboxydimethylamide (XIV).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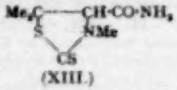
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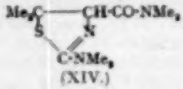
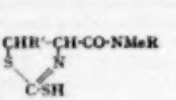

(XIV.)

This formed a water-soluble methiodide which also was not reduced to a thiazolidine by amalgamated aluminium. No analogue of the thiazoline (XII; R = H) could be obtained from 2-mercapto-4-*cyclo*pentylidene-5-thiazolinone, for, with ammonia, this compound gave 2-thio-5-*cyclo*pentylidenehydantoin.

Further observations showed more clearly that the new reaction with dimethylamine was limited in scope, for 2-mercapto-4-*iso*butylidene-5-thiazolinone (VI; R = Pr^i, R′ = H) with ammonia or dimethylamine gave 2-mercapto-5-*iso*propylthiazoline-4-carboxyamide (III; R = Pr^i, R′ = H) or -dimethylamide (XV; R = Me, R′ = Pr^i). Similarly, 2-mercapto-4-benzylidene-5-thiazolinone (VI; R = Ph, R′ = H) with dimethylamine gave 2-mercapto-5-phenylthiazoline-4-carboxydimethylamide (XV; R = Me, R′ = Ph), and again no basic product was obtained; with methylamine, the same benzylidenethiazolinone yielded two products, one of which was 2-thio-3-methyl-5-benzylidenehydantoin (XVI; R = Me), the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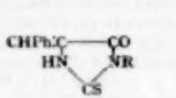
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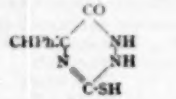
(XVII.)

other being the methylamide (XV; R = H, R′ = Ph). Again, from the reaction between the benzylidenethiazolinone and aniline, two isomeric compounds were isolated: one of these was the known 2-thio-3-phenyl-5-benzylidenehydantoin (XVI; R = Ph), and the other showed ultra-violet absorption indicating it to be probably the stereoisomeride thereof. 2-Thio-3-phenyl-5-*iso*butylidenehydantoin was isolated from the reaction between 2-mercapto-4-*iso*butylidene-5-thiazolinone (VI; R = Pr^i, R′ = H) and aniline; one form only was detected, as also from 2-thio-3-phenyl-5-*p*-nitrobenzylidenehydantoin, obtained in a similar way from the corresponding thiazolinone (VI; R = *p*-NO_2·C_6H_4, R′ = H).

2-Mercapto-4-*p*-methoxybenzylidene-5-thiazolinone (VI; R = *p*-Me·OC_6H_4, R′ = H) with methanolic pyridine or 2-aminopyridine slowly afforded methyl 2-thio-5-*p*-methoxyphenylthiazolidine-4-carboxylate (II; R = *p*-MeO·C_6H_4). In a similar fashion methyl 2-thio-5-phenyl- (II; R = Ph), -5-(2-furyl)- (II; R = C_4H_3O) and -5-*p*-nitrophenyl-thiazolidine-4-carboxylate (II; R = *p*-NO_2·C_6H_4) were prepared. For the last two compounds, this method is the only one at present available, and it appears to offer a convenient route to several otherwise inaccessible aminomercapto-acids.

The reaction between 2-mercapto-4-benzylidene-5-thiazolinone (VI; R = Ph, R′ = H) and hydrazine gave a high-melting yellow compound of the empirical formula $C_{10}H_9ON_3S$, which was characterized as its monomethyl derivative and may be 3-mercapto-6-keto-5-benzylidene-1 : 2 : 5 : 6-tetrahydro-1 : 2 : 4-triazine (XVII).

Experimental.

1-*Amino*-2-*mercapto*-2-*phenylpropionamide Hydrochloride*.—2-Mercapto-5-phenylthiazoline-4-carboxyamide (10 g.) (Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337) in 2N-aqueous sodium hydroxide (25 c.c.) was treated with methyl sulphate (5·6 g.) and kept at 0° for 12 hours. *2-Methylthio-5-phenylthiazoline-4-carboxyamide* (6 g.), which separated, crystallized from aqueous methanol as hexagonal plates, m. p. 93° (Found: C, 51·9; H, 5·1. $C_{11}H_{12}ON_2S_2$ requires C, 52·4; H, 5·1%). Clean aluminium foil (6 g.) was amalgamated in 2% aqueous mercuric chloride for 10 minutes and washed with water and methanol. To it was added a solution of the 2-methylthio-derivative (3 g.) in ethanol (100 c.c.), methanethiol being evolved. When reaction was complete, the liquid was boiled and filtered hot, and the alumina washed with boiling ethanol (50 c.c.). The filtrate and washings were evaporated to 50 c.c. and kept at 0° until separation of *5-phenylthiazolidine-4-carboxyamide* (1 g.) was complete. It separated from water as colourless rods, m. p. 180° (Found: N, 13·1. $C_{10}H_{12}ON_2S$ requires N, 13·5%). It was soluble in hot 2N-hydrochloric acid, the *hydrochloride* separating on cooling as short colourless needles, m. p. 223—224° (decomp.) (Found: C, 48·9; H, 5·7. $C_{10}H_{13}ON_2S.HCl$ requires C, 49·1; H, 5·4%). A hot solution of the thiazolidine (150 mg.) in water (15 c.c.) was poured into hot 5% aqueous mercuric chloride (20 c.c.), a copious white curd separating and formaldehyde being evolved. The

mercaptide was washed with water, dried, and decomposed by passage of hydrogen sulphide into the methanol suspension. Mercuric sulphide was removed and the filtrate evaporated to dryness. The residue was dissolved in dry methanol, the solution filtered, and the product (70 mg.) precipitated with ether. *1-Amino-2-mercapto-2-phenylpropionamide hydrochloride* separated from methanol–ether as a methanolate in plates, m. p. 227—229° (decomp.) (Found: C, 45·2; H, 6·2. $C_9H_{11}ON_2S,HCl,CH_4O$ requires C, 45·0; H, 6·4%). In aqueous sodium hydrogen carbonate, the compound gave a transient purple colour with ferric chloride, which became deep red, slowly fading.

Reaction of Ammonia with 2-Mercapto-4-p-methoxybenzylidenethiazolin-5-one.—A solution of the thiazolinone (18 g.) in aqueous ammonia (50 c.c.) (*d* 0·880) was heated on a steam-bath for 5 minutes, diluted with water (100 c.c.), and acidified after 1 hour with concentrated hydrochloric acid. The pale yellow powder (18 g.) was extracted twice with boiling water (1 l.), leaving a white residue (3·5 g.), m. p. 220°. The extracts deposited pale yellow plates of *α-2-mercapto-5-p-methoxyphenylthiazoline-4-carboxyamide* (11 g.), m. p. 175° (Found: C, 49·4; H, 4·4. $C_{11}H_{12}O_3N_2S_2$ requires C, 49·3; H, 4·5%). The water-insoluble residue of the *β-form* of the amide recrystallized from glacial acetic acid as colourless needles (3 g.), m. p. 223—224° (decomp.) (Found: C, 49·4; H, 4·7%).

5-p-Methoxyphenylthiazolidine-4-carboxyamide.—A solution of the above α-form (8 g.) in 2*N*-potassium hydroxide (16 c.c.) was diluted to 50 c.c. with crushed ice, treated with methyl sulphate (3·5 g.), and kept at 0° for 12 hours. *2-Methylthio-5-p-methoxyphenylthiazoline-4-carboxyamide* crystallized from aqueous ethanol as colourless needles (4·1 g.), m. p. 90° (Found: C, 51·6; H, 5·0. $C_{12}H_{14}O_2N_2S_2$ requires C, 51·1; H, 5·0%). The methylthio-derivative (2 g.) was reduced in methanol (50 c.c.) with amalgamated aluminium (4 g.) to give *5-p-methoxyphenylthiazolidine-4-carboxyamide* (0·8 g.), which formed colourless rods (from water), m. p. 180° (Found: C, 54·7; H, 5·6. $C_{11}H_{14}O_2N_2S$ requires C, 54·3; H, 5·9%).

Action of Nitrous Acid on 5-p-Methoxyphenylthiazolidine-4-carboxyamide.—To a solution of the thiazolidine (0·5 g.) in 2*N*-hydrochloric acid (5 c.c.) at 5° was added a cold solution of sodium nitrite (0·14 g.) in water (5 c.c.). After 1 hour at room temperature, the solution was neutralized with sodium hydrogen carbonate, *5-p-methoxyphenylthiazolidine-4-carboxyamide 1-oxide* (0·3 g.) separating. The compound crystallized from aqueous methanol in short needles, m. p. 186° (Found: C, 51·8; H, 5·6. $C_{11}H_{14}O_3N_2S$ requires C, 52·0; H, 5·6%).

Reaction of Ammonia with 2-Mercapto-4-p-acetoxybenzylidene-5-thiazolinone.—The deep-red solution of 2-mercapto-4-*p*-acetoxybenzylidene-5-thiazolinone (10 g.) in aqueous ammonia (*d* 0·88) (30 c.c.) was heated on the steam-bath for 1 hour and cooled to 0° for 2 hours. The scarlet crystals (0·8 g.) became yellow at 150° and melted at 308° (decomp.). The product was dissolved in warm glacial acetic acid, whereupon a voluminous yellow precipitate appeared almost immediately. 2-Thio-4-*p*-hydroxybenzylidenehydantoin separated from hot water as yellow needles, m. p. 306°, of a hemihydrate (Found: C, 52·4; H, 4·0; N, 12·1. Calc. for $C_{10}H_8O_3N_2S,0·5H_2O$: C, 52·1; H, 4·1; N, 12·2%). Boyd and Robson (*Biochem. J.*, 1935, **29**, 542) give m. p. 305° for the anhydrous material.

The filtrate from the scarlet product above was acidified with concentrated hydrochloric acid, giving an oil. After 18 hours at 0° the aqueous layer was decanted and the residue triturated with a little ethyl acetate, one *isomeride* of *2-mercapto-5-p-hydroxyphenylthiazoline-4-carboxyamide* (2·1 g.), m. p. 234°, remaining insoluble. This crystallized from ethanol–light petroleum (b. p. 60—80°) as colourless rhombohedra, m. p. 234° (Found: C, 47·9; H, 4·2; N, 10·6. $C_{10}H_{10}O_2N_2S_2$ requires C, 47·3; H, 4·0; N, 11·0%). The amide was hydrolysed to the corresponding acid (Cook, Harris, Pollock, and Swan, *loc. cit.*).

Other Preparations of 2-Thio-4-p-hydroxybenzylidenehydantoin.—(*a*) 2-Thio-4-*p*-acetoxybenzylidene-5-thiazolinone (1 g.) was dissolved in 0·5*N*-potassium hydroxide (9 c.c.) and shaken with methyl sulphate (0·5 g.). *2-methylthio-4-p-acetoxybenzylidene-5-thiazolinone* separating. The product separated from a little methanol as yellow plates and needles, m. p. 114° (Found: C, 53·6; H, 3·9. $C_{13}H_{11}O_3NS_2$ requires C, 53·3; H, 3·75%). A suspension of this compound (1 g.) in concentrated aqueous ammonia (10 c.c.) was heated at 100° for 1 hour, while methanethiol was evolved. After the mixture had been cooled to 0° for 2 hours, the scarlet material previously obtained (0·6 g.) was removed, treated with warm acetic acid, and recrystallized from water as yellow needles, m. p. and mixed m. p. 307—308°.

(*b*) Glycine (1·5 g.), potassium thiocyanate (2·5 g.), *p*-hydroxybenzaldehyde (3·5 g.), and acetic anhydride (10 c.c.) reacted violently when warmed. The mixture was heated for 1 hour, cooled, and triturated with water. The yellow solid (0·7 g.), when warmed with concentrated aqueous ammonia, gave the scarlet material above, having a transition point at 140—150° and m. p. 303—305° (decomp.).

Reaction of Ammonia with 2-Mercapto-4-(2-furfurylidene)-5-thiazolinone.—Piperidine (0·1 c.c.) was added to a solution of redistilled furfuraldehyde (18 g.) and 2-mercapto-5-thiazolinone (25 g.) in boiling glacial acetic acid (200 c.c.). After 2 hours, *2-mercapto-4-(2-furfurylidene)-5-thiazolinone* (28 g.) was removed, and a further 2 g. were obtained by dilution of the mother-liquor with water (1 l.). The product crystallized from glacial acetic acid as golden plates, m. p. 186° (Found: C, 45·5; H, 2·5. $C_7H_5O_3NS_2$ requires C, 45·5; H, 2·4%). A solution of the thiazolinone (15 g.) in aqueous ammonia (*d* 0·880) was heated at 100° during 1 hour and kept at 0° for 1 hour. 2-Thio-4-(2-furfurylidene)hydantoin (3·5 g.) was recrystallized from glacial acetic acid and then from water, forming pale yellow needles, m. p. 250° (Found: C, 49·6; H, 3·1; N, 14·3. Calc. for $C_8H_6O_3N_2S$: C, 49·5; H, 3·1; N, 14·4%). Deulofeu (*Anal. Asoc. Quim. Argentina*, 1932, **20**, 190; *Z. physiol. Chem.*, 1932, **204**, 214) gives m. p. 250—251°. The compound gave a bright green colour in warm concentrated sulphuric acid. The filtrate from this material, when acidified with concentrated hydrochloric acid, gave an oil, which solidified to a yellow powder (10·5 g.), m. p. 170—172°. *2-Mercapto-5-(2-furyl)thiazoline-4-carboxyamide* crystallized from water as colourless laths, m. p. 174—176° (Found: C, 42·5; H, 3·6. $C_8H_8O_3N_2S_2$ requires C, 42·1; H, 3·5%).

Alternative Preparations of 2-Thio-4-(2-furfurylidene)hydantoin.—2-Mercapto-4-(2-furfurylidene)-5-thiazolinone (4 g.) was methylated in the usual way with diazomethane to give the *methylthio*-compound (4 g.), which separated from aqueous methanol in yellow hair-like needles, m. p. 74° (Found: C, 47·9; H, 3·2; *N*, 6·0. $C_8H_7O_3NS_2$ requires C, 48·0; H, 3·1; *N*, 6·2%). When treated with aqueous ammonia

in the same way as the *p*-acetoxybenzylidene compound, this methylthio-derivative (3 g.) gave 2-thio-4-(2-furfurylidene)hydantoin (1·2 g.) which, on recrystallization from water, formed yellow needles, m. p. and mixed m. p. with the previous material, 250°. The hydantoin (1 g.) was shaken with 0·5*N*-potassium hydroxide, a potassium salt separating. Methyl sulphate (0·6 g.) was added, and, after 1 hour's shaking, the 2-*methylthio*-derivative (0·6 g.) was collected and recrystallized from aqueous methanol as short yellow needles, m. p. 220° (Found: C, 51·6; H, 3·7. $C_9H_8O_3N_2S$ requires C, 51·9; H, 3·9%). Furfuraldehyde (3 g.), glycine (1·5 g.), potassium thiocyanate (2·5 g.), and acetic anhydride (10 c.c.) were heated at 100° to give a dark brown oil which on being stirred with water yielded the thiohydantoin (1·4 g.). Recrystallization from water gave yellow needles, m. p. and mixed m. p. with the previous material, 250°.

5-(2-Furyl)thiazolidine-4-carboxyamide.—2-Mercapto-5-(2-furyl)thiazoline-4-carboxyamide (10 g.), dissolved in 2*N*-potassium hydroxide (22 c.c.), was shaken for 0·5 hour with methyl sulphate (4·8 g.), an oil separating. The mixture was kept at 0° overnight and the solid (6·2 g.) recrystallized from aqueous methanol as pale yellow plates, m. p. 103° (Found: C, 44·5; H, 4·1. $C_9H_{10}O_3N_2S_2$ requires C, 44·6; H, 4·1%). The *methylthio*-derivative (5 g.) in methanol (300 c.c.) was added to amalgamated aluminium prepared from aluminium foil (10 g.). Methanethiol was evolved and, after refluxing of the mixture, the alumina was filtered off and the combined filtrates and washings were evaporated to 50 c.c. and kept at 0°; the product (2·5 g.), m. p. 107°, separated slowly. *5-(2-Furyl)thiazolidine-4-carboxyamide* formed long colourless rods, m. p. 108°, from hot ethanol (Found: C, 48·4; H, 5·1. $C_8H_{10}O_3N_2S$ requires C, 48·5; H, 5·1%).

Preparation and Reactions of 2-Mercapto-4-p-nitro- and 2-Mercapto-4-p-dimethylamino-benzylidene-5-thiazolinone.—*p*-Nitrobenzaldehyde (12·5 g.) and 2-mercapto-5-thiazolinone (10 g.) were condensed in boiling glacial acetic acid (200 c.c.) containing morpholine (0·1 c.c.) to give *2-mercapto-4-p-nitrobenzylidene-5-thiazolinone* (15·5 g.), which recrystallized from glacial acetic acid in orange plates, m. p. 220° (decomp.) (Found: C, 45·0; H, 1·9; N, 10·7. $C_{10}H_5O_4N_3S_2$ requires C, 45·1; H, 2·3; N, 10·5%). Methylation in the usual way with ethereal diazomethane gave the *2-methylthio*-compound, which formed short orange needles, m. p. 215°, from acetic acid (Found: C, 47·0; H, 3·0. $C_{11}H_7O_4N_3S_2$ requires C, 47·1; H, 2·9%). 2-Mercapto-4-*p*-nitrobenzylidene-5-thiazolinone (2 g.), in aqueous ammonia (*d* 0·880) (15 c.c.) was heated at 100° for 0·5 hour. The *substance* (0·8 g.) was recrystallized from ethanol as purple-red prisms, m. p. 265° (decomp.) (Found: C, 54·7; H, 4·3; N, 18·8. $C_{10}H_9ON_3S$ requires C, 54·8; H, 4·1; N, 19·2%). Namjoshi and Dutt (*J. Indian Chem. Soc.*, 1931, **8**, 241) state that 2-thio-4-*p*-aminobenzylidenehydantoin, prepared by the hydrolysis of its diacetyl derivative, forms yellow needles having no m. p. below 285°. The purple material was soluble in concentrated hydrochloric acid; on neutralization, unchanged starting material was recovered.

p-Dimethylaminobenzaldehyde (10 g.), condensed with 2-mercapto-5-thiazolinone (8 g.) in boiling glacial acetic acid (100 c.c.), gave, after dilution with water (700 c.c.), *2-mercapto-4-p-dimethylamino-benzylidene-5-thiazolinone* (12·5 g.) which separated from acetic acid as rectangular red plates, m. p. 208° (Found: C, 54·7; H, 4·3. $C_{12}H_{11}ON_3S_2$ requires C, 54·6; H, 4·3%). The compound was soluble in concentrated hydrochloric acid to give a pale yellow solution, and was recovered, unchanged on diluting the solution. The thiazolinone (2·0 g.) was dissolved in aqueous ammonia (*d* 0·88) (20 c.c.) and heated at 100° for 2 hours. The red mass was chromatographed in ethyl acetate on activated alumina, and the red band eluted with ethyl acetate. Evaporation left 2-thio-4-*p*-dimethylamino-benzylidenehydantoin, m. p. 258°. The compound separated as glistening red needles, m. p. 261° (decomp.) (Found: N, 16·4. Calc. for $C_{12}H_{13}ON_3S$: N, 17·0%). Namjoshi and Dutt (*loc. cit.*) give m. p. 252°. Hydrogen sulphide was passed for 24 hours through a suspension of the thiazolinone (5 g.) in methanol (100 c.c.) containing triethylamine, the product (3 g.) having m. p. 130—132°. *Triethylammonium 2-mercapto-5-p-dimethylaminophenylthiazoline-4-thiocarboxylate* separated from methanol as pale yellow plates, m. p. 133° (decomp.) (Found: C, 54·0; H, 7·3; N, 10·9. $C_{18}H_{30}ON_3S_3$ C, 54·1; H, 7·3; N, 10·5%).

2-Mercapto-4-isopropylidene-5-thiazolinone.—Anhydrous zinc chloride (20 g.) and 2-mercapto-5-thiazolinone (20 g.) were heated in acetone (130 c.c.) under reflux for 5 hours. The bright green solution was kept at 0° for 4 hours, to give 2-mercapto-4-*iso*propylidene-5-thiazolinone (16 g.) as bright yellow needles, m. p. and mixed m. p. with authentic material, 211°. A further crop (2 g.), m. p. 208—210°, was obtained by diluting the filtrate with water (130 c.c.).

2-Mercapto-5 : 5-dimethylthiazoline-4-carboxyamide.—2-Mercapto-4-*iso*propylidene-5-thiazolinone (15 g.) was dissolved in aqueous ammonia (*d* 0·88) (100 c.c.), and after 0·5 hour at 100° the solution was cooled and acidified. On stirring, the oil gave the *carboxyamide* as a white powder (15·6 g.), which recrystallized from ethyl acetate–light petroleum (b. p. 40—60°) as small colourless prisms and needles, m. p. 145° (Found: C, 38·3; H, 5·4; N, 14·5. $C_8H_{14}ON_2S_2$ requires C, 37·9; H, 5·3; N, 14·7%). Methyl sulphate (7 c.c.) was added to a solution of the 2-mercaptothiazoline (12 g.) in 2*N*-potassium hydroxide (75 c.c.), whereupon the product (9 g.) separated. *2-Methylthio-5 : 5-dimethylthiazoline-4-carboxyamide* separated from acetone–light petroleum (b. p. 40—60°) as sparkling rhombic plates, m. p. 206° (Found: N, 13·3. $C_7H_{12}ON_2S_2$ requires N, 13·7%). The methylthio-derivative (1·4 g.) in methanol (40 c.c.) was added to amalgamated aluminium foil (from 0·5 g.). After the initial reaction, the methanolic solution was boiled under reflux for 10 minutes and filtered hot. The alumina was extracted with boiling methanol (2 × 20 c.c.), and the combined filtrates and washings were evaporated to 20 c.c. and kept at 0° for 24 hours. Crude *2-thio-3 : 5 : 5-trimethylthiazolidone-4-carboxyamide* (0·5 g.) had m. p. 198—200°, undepressed on admixture with starting material. Recrystallized from water, it formed long colourless rods, m. p. 200° (Found: C, 41·4; H, 6·1; N, 13·4. $C_7H_{12}ON_2S_2$ requires C, 41·2; H, 5·9; N, 13·7%). The starting material dissolved in water only on prolonged boiling, methanethiol being evolved but no crystalline material separating on cooling.

Reaction of 2-Mercapto-4-isopropylidene-5-thiazolinone with Dimethylamine. [With E. FREDERIKSEN].—A solution of the thiazolinone (5 g.) in 33% aqueous dimethylamine (25 c.c.) was heated for 0·5 hour at 100°, and cooled. The product (3·7 g.), m. p. 185° (decomp.), was removed. It was insoluble in alkali and readily soluble in acid and was recrystallized from ethanol, *2-dimethylamino-5 : 5-dimethyl-*

thiazoline-4-carboxydimethylamide forming colourless crystals, m. p. 185° (Found: C, 52·1; H, 8·4. $C_{12}H_{22}ON_2S$ requires C, 52·4; H, 8·3%). The compound, on treatment with methyl iodide in acetone, yielded the insoluble *methiodide* which crystallized from water–acetone as a hemihydrate, m. p. 110—111° (Found: C, 34·7; H, 6·2. $C_{11}H_{22}ON_2SI,0·5H_2O$ requires C, 34·6; H, 6·1%).

2-Thio-4-cyclopentylideneh ydantoin.—A solution of 2-mercapto-4-*cyclo*pentylidene-5-thiazolinone (1 g.; Cook and Pollock, *loc. cit.*) in aqueous ammonia (*d* 0·880) (5 c.c.) was heated at 100° for 0·5 hour. The *thiohydantoin* was recrystallized from acetic acid, forming colourless needles, m. p. 252° (decomp.) (Found: C, 52·2; H, 5·6; N, 15·0. $C_8H_{10}ON_2S$ requires C, 52·7; H, 5·6; N, 15·4%).

Reactions with 2-Mercapto-4-isobutylidene-5-thiazolinone. The thiazolinone (2 g.; Billimoria and Cook, *J.*, 1949, 2323) in aqueous ammonia (*d* 0·880) (20 c.c.) was heated at 100° for 1 hour and then kept at room temperature for 18 hours. *2-Mercapto-5-isopropylthiazoline-4-carboxyamide* (1·2 g.) formed colourless plates, m. p. 131°, from hot water (Found: C, 41·5; H, 5·9; N, 13·7. $C_7H_{12}ON_2S_2$ requires C, 41·2; H, 5·9; N, 13·7%). The original thiazolinone was warmed in 30% aqueous dimethylamine (20 c.c.) for 1 hour, and the solution cooled and acidified with hydrochloric acid. The corresponding *dimethylamide* (1·5 g.) recrystallized from hot water as colourless plates, m. p. 144° (Found: C, 46·3; H, 6·9. $C_9H_{16}ON_2S_2$ requires C, 46·6; H, 7·0%). A solution of 2-mercapto-4-*iso*butylidene-5-thiazolinone (2·0 g.) and aniline (1·0 g.) in methanol (30 c.c.) was refluxed for 24 hours. The colourless gum remaining on evaporation was treated with 2*N*-hydrochloric acid and dissolved in acetone (10 c.c.). *2-Thio-3-phenyl-5-isobutylidenehydantoin* was precipitated on addition of water (20 c.c.) and separated from aqueous methanol in colourless plates, m. p. 209° (Found: C, 63·1; H, 5·8. $C_{13}H_{14}ON_2S$ requires C, 63·4; H, 5·7%).

Reactions with 2-Mercapto-4-benzylidene-5-thiazolinone.—The thiazolinone (2 g.) in 40% aqueous dimethylamine (10 c.c.) was heated at 100° for 0·5 hour, cooled, diluted with water (10 c.c.), and filtered. The sticky residue was extracted with boiling methanol (20 c.c.), the mixture cooled to 0° for 1 hour, and the product (0·7 g.), m. p. 190°, filtered off. 2-Thio-3-methyl-5-benzylidenehydantoin recrystallized from acetic acid as pale yellow needles, m. p. 207° (Found: C, 60·7; H, 4·3; N, 13·0. Calc. for $C_{11}H_{10}ON_2S$: C, 60·6; H, 4·6; N, 12·8%). The filtrate from the reaction mixture was acidified with hydrochloric acid, and the product crystallized from aqueous methanol as brown needles (0·4 g.), m. p. 165°, of the methylamide which probably contained a small amount of the hydantoin as impurity. 2-Mercapto-4-benzylidene-5-thiazolinone (2 g.) was heated at 100° in 30% aqueous dimethylamine (10 c.c.) for 0·5 hour. The dark oil was extracted with chloroform (20 c.c.) and the aqueous layer extracted with chloroform (20 c.c.) and acidified with 2*N*-hydrochloric acid to give a sticky brown solid, which was rubbed with methanol to give *2-mercapto-5-phenylthiazoline-4-carboxydimethylamide* (0·5 g.); the last recrystallized from aqueous methanol as colourless needles, m. p. 191—192° (Found: C, 54·2; H, 5·4. $C_{12}H_{14}ON_2S_2$ requires C, 54·1; H, 5·3%). The combined chloroform extracts were evaporated to leave an oil which was stirred with 2*N*-hydrochloric acid to give a further quantity of the dimethylamide (0·9 g.), m. p. and mixed m. p. 191°. 2-Mercapto-4-benzylidenethiazolin-5-one (3·0 g.) and aniline (10 c.c.) were heated together at 100° for 0·5 hour, and the mixture cooled to 0° and treated with 2*N*-hydrochloric acid. The yellow oil gave, on trituration with methanol (10 c.c.), a pale yellow solid, which on treatment with hot acetic acid (50 c.c.) and cooling yielded *trans*-2-thio-3-phenyl-5-benzylidenehydantoin (1·2 g.); this separated from acetic acid as pale yellow needles, m. p. 206—207° (Found: C, 69·0; H, 4·3; N, 9·6. Calc. for $C_{16}H_{12}ON_2S$: C, 68·6; H, 4·3; N, 10·0%). $\lambda_{max.}$ (in methanol): 248 and 370 mμ., $E^{1\%}_{1cm.}$ = 470 and 1220 respectively.

The acetic acid filtrate was diluted with water (50 c.c.) to give the *cis-isomer*, which recrystallized from aqueous methanol as fine yellow needles, m. p. 160° (Found: C, 68·3; H, 4·8; N, 10·5%). $\lambda_{max.}$ (in methanol) 228, 249, 280, and 370 mμ., $E^{1\%}_{1cm.}$ = 530, 500, 530, and 800 respectively.

The *trans*-isomer (1·0 g.) in 10% sodium hydroxide solution (30 c.c.) was treated with methyl sulphate; the resultant 2-methylthio-derivative (1·0 g.) recrystallized from methanol as pale yellow prisms, m. p. 151° (Found: C, 68·6; H, 4·9; N, 9·4. Calc. for $C_{17}H_{14}ON_2S$: C, 68·4; H, 4·8; N, 9·5%).

Reaction between Aniline and 2-Mercapto-4-p-nitrobenzylidene-5-thiazolinone.—The thiazolinone (3·5 g.) was heated with aniline (10 c.c.) at 100° for 1 hour, and the mixture cooled to 0° and treated with 2*N*-hydrochloric acid. Treatment of the gummy product with methanol gave *2-thio-3-phenyl-5-p-nitrobenzylidenehydantoin* (2·7 g.) which from aqueous acetic acid formed a hemihydrate, m. p. 266° (decomp.) (Found: C, 57·7; H, 3·8; N, 12·4. $C_{16}H_{11}O_3N_3S,0·5H_2O$ requires C, 57·5; H, 3·6; N, 12·6%).

Reactions with 2-Aminopyridine and Pyridine.—2-Mercapto-4-benzylidene-5-thiazolinone (2·1 g.) and 2-aminopyridine (0·95 g.) were heated in refluxing methanol (30 c.c.) for 12 hours. Dilution with water (60 c.c.) gave a gum which yielded *methyl 2-thio-5-phenylthiazolidine-4-carboxylate* (2·0 g.) on crystallization from ether–light petroleum (b. p. 40—60°). The compound separated from aqueous methanol as colourless hexagonal plates, m. p. 109° (Found: C, 52·6; H, 4·4; N, 5·5. $C_{11}H_{11}O_2NS_2$ requires C, 52·2; H, 4·4; N, 5·5%).

The original thiazolinone (1·0 g.) and pyridine (0·5 c.c.), heated in refluxing methanol (10 c.c.) for 12 hours, acidified with acetic acid and diluted with water (30 c.c.) gave a gum which was crystallized from aqueous methanol to yield the methyl ester (0·8 g.) identical with the material described above.

A solution of 2-mercapto-4-*p*-methoxybenzylidene-5-thiazolinone (3·8 g.) and 2-aminopyridine (1·4 g.) in refluxing methanol (25 c.c.) was heated for 12 hours and worked up in the same way, to give a gum which solidified under methanol to give methyl 2-thio-5-*p*-methoxyphenylthiazolidine-4-carboxylate (2·7 g.), m. p. and mixed m. p. with authentic material, 110° after recrystallization from chloroform–light petroleum (b. p. 40—60°) (Cook, Harris, Pollock, and Swan, *loc. cit.*).

2-Mercapto-4-(2-furfurylidene)-5-thiazolinone (2·5 g.) and 2-aminopyridine (1·5 g.), heated in refluxing methanol (20 c.c.) for 12 hours and diluted with water (30 c.c.), gave a black oil, which on repeated precipitation from aqueous methanol (charcoal) yielded *methyl 2-thio-5-(2-furyl)thiazolidine-4-carboxylate* (0·5 g.) as yellow rods or prisms, m. p. 89° (Found: C, 44·7; H, 3·9; N, 5·8. $C_9H_9O_3NS_2$ requires C, 44·5; H, 3·7; N, 5·8%).

A solution of 2-mercapto-4-*p*-nitrobenzylidene-5-thiazolinone (5·2 g.) and 2-aminopyridine (1·8 g.) was heated in methanol (50 c.c.) for 12 hours and diluted with water (50 c.c.), to give a yellow gum which crystallized under methanol. *Methyl 2-thio-5-p-nitrophenylthiazolidine-4-carboxylate* (4·8 g.) separated from ethanol as pale yellow rods, m. p. 148—149° (Found: C, 44·3; H, 3·5; N, 9·6. $C_{11}H_{10}O_4N_2S_2$ requires C, 44·3; H, 3·4; N, 9·4%). The thiazolidine (2·9 g.), treated in 5% sodium hydroxide solution (10·5 c.c.) with methyl sulphate (0·6 c.c.) and kept at 0° for 24 hours, yielded a clear solution which, on acidification and stirring of the resultant sticky solid under methanol, yielded *2-methylthio-5-p-nitrophenylthiazoline-4-carboxylic acid* (2·1 g.). The acid recrystallized from methanolic acetic acid in massive golden cubes, m. p. 167° (Found: C, 44·6; H, 3·7; N, 9·2. $C_{11}H_{10}O_4N_2S_2$ requires C, 44·3; H, 3·4; N, 9·4%).

5-Mercapto-6-keto-5-benzylidene-1:2:5:6-tetrahydro-1:2:4-triazine.—2-Mercapto-4-benzylidene-5-thiazolinone (1·8 g.) and hydrazine hydrate (2 c.c.) were heated together in methanol (10 c.c.) under reflux for 1 hour, hydrogen sulphide being evolved. The solution was diluted with ice, which precipitated a sticky solid (*A*). This crystallized under 2*N*-hydrochloric acid to give the *triazine* (0·2 g.), which was recrystallized from acetic acid as yellow rods, m. p. 251°. The hydrochloric acid filtrate gave a small precipitate, m. p. >300°, on neutralization with sodium hydrogen carbonate. The original aqueous solution (decanted from solid *A*) was kept at room temperature for 48 hours, while further material (0·7 g.), m. p. 250°, alone and mixed with the previously-obtained material, separated (Found: C, 54·8; H, 4·4. $C_{11}H_9ON_3S$ requires C, 54·8; H, 4·1%). Methylation in alkaline solution gave the *3-methylthio*-derivative, which recrystallized from aqueous methanol as yellow rods or prisms, m. p. 227° (decomp.) (Found: C, 56·6; H, 4·9. $C_{11}H_{11}ON_3S$ requires C, 56·7; H, 4·8%).

We thank the Department of Scientific and Industrial Research for Maintenance Grants (to G. D. H. and J. R. A. P.) and Sir Ian Heilbron, D.S.O., F.R.S., for his continued interest and encouragement.

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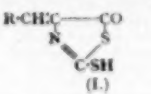
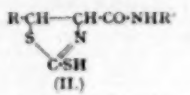
387. *Studies in the Azole Series. Part XXXII. Syntheses of Peptides of Substituted Cysteines.*

By A. H. Cook and J. R. A. Pollock.

2-Mercapto-4-arylidene- and -alkylidene-5-thiazolinones (I) react with amino-acids or derivatives thereof, to give 5-substituted 2-mercaptothiazoline-4-carboxylic acid peptides or their derivatives (VI). The peptide derivatives can be degraded in satisfactory yield to 5-substituted thiazolidine-4-carboxylic acid peptide derivatives, *e.g.*, (X), which can be split to give formaldehyde and peptides of substituted cysteines.

Amines have been shown (see Parts VII, XXIV, and XXXI, *J.*, 1948, 1337; 1949, 3007; 1950, 1892) to react with 2-mercapto-4-alkylidene- and -arylidene-5-thiazolinones (I) (2-thio-4-alkylidene- and -arylidene-5-thiazolidones) to afford 2-mercapto-5-alkyl- and -5-aryl-thiazoline-4-carboxyamides (II), which may be regarded as derivatives of substituted cysteine amides, to which they can in fact be degraded. The present paper deals with a similar sequence of reactions which follow the combination of amino-acids or their derivatives and the thiazolinones (I). The


(I.)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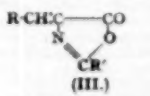
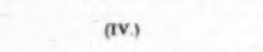

(III.)

primary reaction may be compared with that occurring between the azlactones (III) and amino-acids, which has been studied by Bergmann *et al.* (*Annalen*, 1926, **449**, 277; 1927, **458**, 40; *J. Biol. Chem.*, 1938, **124**, 321; 1939, **129**, 587), who have thus obtained the dehydropeptides (IV). In the case of the thiazolinones, the intermediate comparable with (IV) is the dithiocarbamic acid (V), which appears to cyclise to the 2-mercapto-thiazoline system as in (VI).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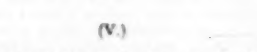
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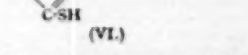
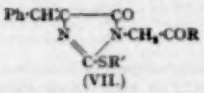
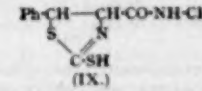

(VI.)

Glycine ethyl ester reacted smoothly with 2-mercapto-4-benzylidene-5-thiazolinone (I; R = Ph) to yield a mixture from which ethyl 2-mercapto-5-phenyl-Δ^1-thiazoline-4-carboxyamidoacetate (VI; R = Ph, R′ = H, R″ = Et) could be isolated, though in poor yield. Analogy with the reaction between (I; R = Ph) and methylamine (Part XXXI, *loc. cit.*)

suggested that ethyl 2-thio-5-benzylidenehydantoin-3-acetate (VII; R = OEt, R′ = H) might have arisen as a by-product from this reaction, and this compound was isolated from the methylated reaction mixture as its *S*-methyl derivative (VII; R = OEt, R′ = Me). This

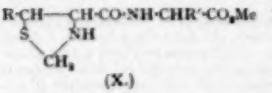

(VII.)

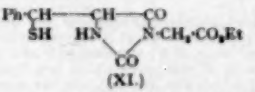
(VIII.)


(IX.)

derivative was identical with a sample prepared by methylating the thiohydantoin prepared from 2-methylthio-4-benzylidene-5-thiazolinone (VIII) and glycine ester. The reaction between aminoacetamide and (I; R = Ph) took a similar course, the chief product being 2-thio-5-benzylidenehydantoin-3-acetamide (VII; R = NH_2, R′ = H), which was characterized as its *S*-methyl derivative, while 2-mercapto-5-phenylthiazoline-4-carboxyamidoacetamide (IX) was also produced, in small yield.

The occurrence of a mixture of compounds in this way could be avoided, it was found, by using as ring-opening agent the amino-acid rather than amino-acid derivatives. When one equivalent each of the sodium salt of glycine and (I; R = Ph) were heated together in water, a material was obtained which appeared to consist of a mixture from which one of the two possible stereoisomeric forms of the acid (VI; R = Ph, R′ = H, R″ = H) was isolated. The presence of the second form was proved by degradation of the crude mixture by treatment of the oily methylation product with amalgamated aluminium. By this means methanethiol was eliminated (cf. Cook, Hunter, and Pollock, Part XXXI, *loc. cit.*) and the product was separable into the two stereoisomeric forms of methyl 5-phenylthiazolidine-4-carboxyamidoacetate (X; R = Ph, R′ = H). A better overall yield resulted from the use of a 50% excess of glycine sodium salt, an apparently pure intermediate (VI; R = Ph, R′ = H, R″ = H) being isolated which gave one form only of the thiazolidine (X; R = Ph, R′ = H). The acid (VI; R = Ph, R′ = H, R″ = H) was treated with ethanolic hydrogen chloride in an attempt to prepare the ethyl ester (VI; R = Ph, R′ = H, R″ = Et), one isomeride of which had already been isolated. However, the product had the empirical formula $C_{14}H_{14}O_4N_2S$ and it was perhaps ethyl 5-α-mercaptobenzylhydantoin-3-acetate (XI).


(X.)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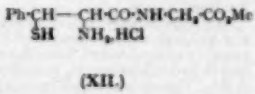
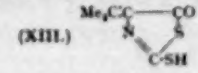

(XII.)

The thiazolidine (X; R = Ph, R′ = H) recalls the amide (II; R = Ph, R′ = H), which has been converted into β-phenylcysteineamide (Cook, Hunter, and Pollock, *loc cit.*); in the same manner, treatment of the new peptide with mercuric chloride caused fission of the thiazolidine ring, yielding formaldehyde and a mercaptide, which was decomposed to yield (*N*-α-amino-β-mercapto-β-phenylpropionyl)glycine methyl ester hydrochloride (XII) in good yield.

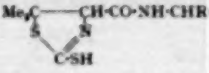
The stereoisomerism of the intermediate 2-mercapto-Δ^4-thiazolines and the corresponding thiazolidines complicates the extension of these reactions. The general reaction involving any α-amino-acid and any alkylidene- or arylidene-thiazolinone must lead to a 2-mercaptothiazoline (VI) containing 3 asymmetric carbon atoms, and thus capable of yielding four optically inactive forms. In a preliminary investigation we therefore used 2-mercapto-4-*iso*propylidene-5-thiazolinone (XIII), the rearrangement products of which possessed only two asymmetric centres. 2-Mercapto-5 : 5-dimethylthiazoline-4-carboxyamidoacetic acid (XIV; R = H) was readily prepared by reaction of (XIII) with glycine. DL-Alanine rapidly gave a mixture of two compounds which were readily separated, although only one isomeride (XIV; R = Me) was obtained crystalline. Further simplification was achieved by use of an excess of the amino-acid sodium salt which favoured the production of one only of the isomers of (VI; R = Ph, R′ = H, R″ = H). When this method was applied to the reaction between (I; R = Ph) and DL-alanine, the product, presumably a mixture of the two acids (VI; R = Ph, R′ = Me, R″ = H), was an intractable gum. However, methylation gave an oily methyl derivative which, on reduction in the usual way, yielded a mixture of two isomeric esters (X; R = Ph, R′ = Me), both isolated in a crystalline condition.

In a further study, intermediates were used where the 5-position carried only one aliphatic substituent. A convenient starting material was 2-mercapto-4-*iso*butylidene-5-thiazolinone (I;

R = Pr^{i}) which reacted rapidly with the sodium salt of glycine: one isomeride only of 2-mercapto-5-*iso*propylthiazoline-4-carboxyamidoacetic acid (VI; R = Me_2CH, R′ = H,



(XIII.)



(XIV.)

R″ = H) was obtained. This with methyl sulphate gave 2-methylthio-5-*iso*propylthiazoline-4-carboxyamidoacetic acid, which gave an oily ester. The ester, reduced with amalgamated aluminium, afforded methyl 5-*iso*propylthiazolidine-4-carboxyamidoacetate (X; R = Pr^{i}, R′ = H), in an overall yield of 21% from *iso*butyraldehyde.

Experimental.

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and Glycine Ethyl Ester.—The thiazolinone (2·2 g.) was heated under reflux for 2 hours with glycine ethyl ester hydrochloride (1·5 g.) dissolved in a mixture of N-sodium hydroxide (10 c.c.) and methanol (20 c.c.). The solution was cooled to 0° and the crystalline material (0·7 g.; m. p. 135°) was washed with ether (10 c.c.): the residue (0·4 g.) had m. p. 170°. *Ethyl 2-mercapto-5-phenylthiazoline-4-carboxyamidoacetate* separated from a little methanol in colourless needles, m. p. 170° (Found: C, 51·3; H, 4·8. $C_{14}H_{14}O_3N_2S_2$ requires C, 51·8; H, 4·9%). In another experiment, the crude reaction product (1 g.; m. p. 135°) was dissolved in N-sodium hydroxide (5 c.c.), and crushed ice was added, followed by methyl sulphate (0·25 c.c.). A white solid (0·5 g.), m. p. 103°, separated after 5 minutes. Recrystallization from aqueous methanol gave *ethyl 2-methylthio-5-keto-4-benzylidene-4 : 5-dihydroglyoxaline-1-acetate* as colourless needles, m. p. 121° (Found: N, 9·2. $C_{15}H_{16}O_3N_2S$ requires N, 9·2%).

2-Mercapto-4-benzylidene-5-thiazolinone (4·4 g.) was dissolved in N-sodium hydroxide (20 c.c.), and methyl sulphate (2·5 g.) was added. The solution was shaken until separation of the 2-methylthio-derivative (4·0 g.) was complete. It recrystallized from methanol (50 c.c.) as long orange needles (2·8 g.), m. p. 124°. To a solution of this compound (1·2 g.) and glycine ethyl ester hydrochloride (0·8 g.) in methanol (50 c.c.) was added N-sodium hydroxide (5 c.c.), and the solution was heated under reflux for 1 hour, methanethiol being evolved. The solution was concentrated to 15 c.c. and cooled to 0° while *ethyl 2-mercapto-5-keto-4-benzylidene-4 : 5-dihydroglyoxaline-1-acetate* (0·8 g.), m. p. 160°, separated. The product was recrystallized from methanol, without change in m. p., as colourless needles (Found: C, 57·8; H, 4·9; N, 9·6. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·9; N, 9·7%). The thiohydantoin (0·5 g.) in N-sodium hydroxide (1·5 c.c.) with methyl sulphate (0·2 c.c.) gave the 2-methylthio-derivative which, recrystallized from aqueous methanol, had m. p. 121°, undepressed on admixture with the compound described above.

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and Glycine.—(*a*) The thiazolinone (2·2 g.) was warmed with a solution of glycine (0·75 g.) in N-sodium hydroxide (10 c.c.) for 1 hour. A small quantity of unchanged thiazolinone (m. p. 211°) was removed, and the filtrate was acidified with concentrated hydrochloric acid, whereby an oil was precipitated which had partly crystallized after 24 hours at 0°. The oil was taken up in ethyl acetate (60 c.c.), and the solution dried and evaporated to 10 c.c. Slow addition of light petroleum (b. p. 60—80°) then precipitated gummy material and colourless crystals; the latter were removed, giving 0·3 g. of material having m. p. 176—182°. Recrystallized from ethyl acetate–light petroleum, *2-mercapto-5-phenylthiazoline-4-carboxyamidoacetic acid* separated as small colourless needles, m. p. 179° (Found: C, 48·3; H, 4·1; N, 9·4. $C_{12}H_{12}O_3N_2S_2$ requires C, 48·6; H, 4·1; N, 9·5%).

(*b*) 2-Mercapto-4-benzylidene-5-thiazolinone (11 g.) was dissolved by warming in a solution of glycine (5·7 g.) in water (20 c.c.) containing sodium hydroxide (3 g.). The solution was acidified at 0° with concentrated hydrochloric acid, and the precipitated oil was rubbed until solidification to a pale yellow powder (2·2 g.; m. p. 170°) was complete. Recrystallized from boiling water, *2-mercapto-5-phenylthiazoline-4-carboxyamidoacetic acid hemihydrate* (11·5 g., 77%) formed colourless thick rods having m. p. 170°. Further crystallization in the same way raised the m. p. to 186° (Found: C, 47·3; H, 4·3; N, 9·4. $C_{12}H_{12}O_3N_2S_2,\frac{1}{2}H_2O$ requires C, 47·2; H, 4·3; N, 9·2%).

Methyl 5-Phenylthiazolidine-4-carboxyamidoacetate.—(*a*) The crude peptide, as obtained in (*a*) above from 2-mercapto-4-benzylidene-5-thiazolinone (2·2 g.), was dissolved in ethyl acetate (30 c.c.), and the solution dried (Na_2SO_4). A solution of diazomethane (0·6 g.) in ether (20 c.c.) was added slowly, nitrogen being evolved. After 3 hours, the solvents were removed *in vacuo* to leave a mobile yellow oil. Clean aluminium foil (0·5 g.) was amalgamated in 3% aqueous mercuric chloride solution for 10 minutes and washed well with water and methanol. To it was added a solution of the yellow oil in methanol (20 c.c.); methanethiol was evolved. The solution was heated under reflux at the end of the reaction, and the alumina filtered off and extracted twice with hot methanol (20 c.c.). The combined filtrates were evaporated to leave a pale yellow oil, which was stirred with a mixture of ether (5 c.c.) and water (5 c.c.), whereupon crystallization commenced in the ethereal layer. The mixture was kept at 0° for 5 hours, colourless needles (0·7 g.), m. p. 126°, separating. The material was extracted with boiling ether (60 c.c.) (extract *A*). The residue (0·3 g.) of the *a-form* of *methyl 5-phenylthiazolidine-4-carboxyamidoacetate* formed colourless needles, m. p. 173°, from hot water (Found: C, 55·8; H, 5·8; N, 10·0. $C_{13}H_{16}O_3N_2S$ requires C, 55·7; H, 5·7; 10·0%). The compound gave a *picrate* which formed yellow prisms, m. p. 170°, from water (Found: N, 13·8. $C_{13}H_{16}O_3N_2S,C_6H_3O_7N_3$ requires N, 12·8%). The ether–water filtrate from the crystallization of the *a*-compound was separated, and the aqueous layer washed with ether. The ethereal extracts were combined with the extract *A*, dried, and evaporated to 5 c.c. Addition of light petroleum (b. p. 60—80°) caused the separation of rosettes of colourless needles (0·2 g.),

m. p 110—112°. These, the *β-form* of the peptide, separated from a little hot water as colourless needles, m. p. 115° (Found : C, 55·8; H, 5·7; N, 10·2%).

(*b*) The peptide hemihydrate (10 g.; m. p. 177°) was suspended in ether (50 c.c.) and treated with a solution of diazomethane (3 g.) in ether (100 c.c.); nitrogen was rapidly evolved. After 3 hours the solution was worked up to a yellow oil and reduced in methanol as recorded in (*a*). Evaporation gave a colourless oil which was stirred with ether (10 c.c.) and water (10 c.c.). After 24 hours at 0°, the above *β*-form (3·5 g., 40%) was filtered off. It had m. p. 112—113°, undepressed on admixture with previously prepared material.

(*c*) The peptide hemihydrate (m. p. 177°; 10·5 g.) in water (20 c.c.) containing sodium hydroxide (2·8 g.) was shaken for 30 minutes with methyl sulphate (3·3 c.c.), giving a clear solution which was acidified cautiously with hydrochloric acid. The precipitated oil was extracted with ethyl acetate (300 c.c.) and the aqueous layer extracted similarly (2 × 50 c.c.). The combined extracts were dried and evaporated to 100 c.c. Attempts to obtain crystalline material from the solution failed. The solution was treated with diazomethane (1·5 g.) in ether (30 c.c.). After 0·5 hour the solution was evaporated, to give a clear yellow oil which was reduced as described in (*a*). The product, worked up as described in (*b*), yielded the *β*-form (4·1 g., 46%), m. p. 113—115°.

Treatment of 2-Mercapto-5-phenylthiazoline-4-carboxyamidoacetic Acid with Ethanolic Hydrogen Chloride.—The thiazoline (1 g.) was kept in saturated ethanolic hydrogen chloride (5 c.c.) at 0° for 3 days, after which the crystalline material (0·3 g.), m. p. 105—108°, was removed. *Ethyl 4-α-mercaptobenzylhydantoin-1-acetate* (?) separated as colourless shining plates, m. p. 114°, from aqueous ethanol (Found : C, 55·5; H, 5·1; N, 9·1. $C_{14}H_{16}O_3N_2S$ requires C, 54·9; H, 5·3; N, 9·2%). The compound gave no colour with aqueous or ethanolic ferric chloride, or with sodium nitroprusside reagent.

1-Amino-2-mercapto-2-γ-phenylpropionylglycine Methyl Ester Hydrochloride.—The *β*-form of the above ester (3·8 g.) was dissolved in hot water (1 l.), and a solution of mercuric chloride in water (500 c.c.) at 60° was rapidly introduced, the solution becoming turbid and formaldehyde being evolved. After 3 hours the curd was filtered off, washed with water, and dried in air at 40° (9·5 g.). The mercaptide (2 g.) was finely powdered and suspended in ethanol, which was then saturated with hydrogen sulphide with vigorous stirring. Mercuric sulphide was removed. A small part of the filtrate, after being boiled to expel hydrogen sulphide, was neutralized with sodium hydrogen carbonate and treated with ethanolic ferric chloride, which produced an intense Prussian-blue colour. The bulk of the solution was evaporated to dryness, giving a pale yellow gum which crystallized on repeated trituration with small quantities of dry ether. After reduction to a fine powder, the material was removed and, while still covered with ether, was transferred to a desiccator and dried over concentrated sulphuric acid *in vacuo*. *1-Amino-2-mercapto-2-phenylpropionylglycine ethyl ester hydrochloride* (0·4 g., 29%) was thus obtained as a colourless hygroscopic hemihydrate, m. p. 90—91° (decomp.) (Found : C, 45·9; H, 6·0; N, 9·0. $C_{13}H_{18}O_3N_2S,HCl,\frac{1}{2}H_2O$ requires C, 45·9; H, 5·8; N, 8·9%).

Reactions with 2-Mercapto-4-isopropylidene-5-thiazolinone.—(*a*) *With glycine.* The thiazolinone (1·7 g.) was suspended in a solution of glycine (0·75 g.) in N-sodium hydroxide (10 c.c.) and heated on the steam bath until a clear solution was obtained. After acidification at 0° with hydrochloric acid, the clear solution was extracted with ethyl acetate (3 × 10 c.c.). The combined extracts were dried and evaporated to 5 c.c. Light petroleum (b. p. 60—80°) was added to precipitate a sticky mass which broke up to give a pale yellow powder (1·7 g.), m. p. 190°. *2-Mercapto-5 : 5-dimethylthiazoline-4-carboxyamidoacetic acid* recrystallized from ethyl acetate–light petroleum (b. p. 40—60°) as minute colourless needles, m. p. 193° (Found : C, 38·9; H, 4·8; N, 11·2. $C_8H_{12}O_3N_2S_2$ requires C, 38·7; H, 4·9; N, 11·3%).

(*b*) *With* DL-*alanine.* To a solution of DL-alanine (4·2 g.) and potassium hydroxide (2·6 g.) in water (20 c.c.) was added 2-mercapto-4-*iso*propylidene-5-thiazolinone (5·4 g.); reaction was rapid and a clear solution obtained after warming for 10 minutes. Acidification at 0° gave a clear solution which was extracted with ethyl acetate (2 × 30 c.c.). The extracts were dried, concentrated to 20 c.c., and cooled to 0°, whereupon *α-(2-mercapto-5 : 5-dimethylthiazoline-4-carboxyamido)propionic acid* (2·3 g., 33%), m. p. 196°, separated. When recrystallized from a little ethyl acetate, the peptide separated as colourless thick needles, m. p. 208° (Found : C, 41·3; H, 5·5; N, 10·5. $C_9H_{14}O_3N_2S_2$ requires C, 41·2; H, 5·4; N, 10·7%). The ethyl acetate filtrates were evaporated to leave a sticky gum, which did not crystallize.

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and DL-*Alanine.*—A suspension of the thiazolinone (11 g.) in a solution of alanine (6·8 g.) in N-potassium hydroxide (75 c.c.) was warmed, the thiazolinone rapidly dissolving. The clear liquid was heated on the steam bath for 1 hour, cooled, and acidified with concentrated hydrochloric acid, whereby a brown oil was precipitated. This was dissolved in ethyl acetate (40 c.c.), the aqueous layer was extracted with ethyl acetate (2 × 30 c.c.), and the combined extracts were dried and evaporated to 20 c.c. Diazomethane (4 g.) in ether (100 c.c.) was slowly added and the solution kept at room temperature overnight. Solvents were evaporated and the remaining pale yellow oil was dissolved in methanol (200 c.c.) and added to amalgamated aluminium foil (6 g.). Methanethiol was evolved. When reduction was complete, the methanolic solution was boiled and filtered hot, and the alumina twice extracted with boiling methanol (200 c.c.). The combined filtrates were evaporated to a colourless oil, which was stirred with water (30 c.c.) and ether (20 c.c.). After 16 hours at 0°, the mixture was filtered (*A*). The product (4 g.), m. p. 90—120°, was dried *in vacuo* and extracted with boiling ether (150 c.c.) (*B*), a residue of colourless needles (1 g.), m. p. 130—150°, remaining. When recrystallized from water, the *α-form* of *methyl α-(5-phenylthiazolidine-4-carboxyamido)propionate* formed colourless needles, m. p. 166° (Found : C, 56·7; H, 6·2; N, 9·8. $C_{14}H_{18}O_3N_2S$ requires C, 57·1; H, 6·2; N, 9·5%). The ethereal filtrate *B*, kept at 0° overnight, yielded a further crop of the impure *α*-form (0·2 g.), m. p. 145—153° (filtrate *C*). The ethereal layer from *A* was combined with *C*, and the whole dried, evaporated to 20 c.c., and diluted with light petroleum (b. p. 40—60°; 200 c.c.), whereafter the *β-form* of the thiazolidine-peptide separated (2·8 g.; m. p. 110—114°). Recrystallized from water, this formed colourless fine needles, m. p. 118° (Found : C, 57·3; H, 6·2; N, 9·6%). A mixture with the *α*-form had m. p. 94—97°. Evaporation of the ether–light petroleum filtrate left a further crop of crude *β*-form (0·9 g.), m. p. 105—107°, giving a total yield of 4·9 g. (33%, based on the original thiazolinone).

Reaction between 2-Mercapto-4-isobutylidene-5-thiazolinone and Glycine.—A solution prepared by stirring the thiazolinone into a hot solution of glycine (5·7 g.) and sodium hydroxide (3·0 g.) in water (50 c.c.) was heated on the steam-bath for 0·5 hour. The solution was acidified at 0° with concentrated hydrochloric acid, a mobile oil separating which when kept at 0° overnight solidified to a crystalline mass, m. p. 40°. *2-Mercapto-5-isopropylthiazoline-4-carboxyamidoacetic acid sesquihydrate* formed colourless plates, m. p. 42°, from a little warm water (Found : C, 37·3; H, 6·1; N, 9·5. $C_9H_{14}O_3N_2S_2,1{\cdot}5H_2O$ requires C, 37·3; H, 5·9; N, 9·7%).

Methyl 5-isoPropylthiazolidine-4-carboxyamidoacetate.—The above sesquihydrate (10 g.) was dissolved in water (30 c.c.) containing sodium hydroxide (2·9 g.), and methyl sulphate (4·9 g.) was added. After 0·5 hour's shaking, a clear solution was obtained, which was acidified with hydrochloric acid. The supernatant liquid was decanted and extracted with ethyl acetate (2 × 100 c.c.), and the extract dried, evaporated to 20 c.c. and diluted with light petroleum (b. p. 40—60°), to give *2-methylthio-5-isopropylthiazoline-4-carboxyamidoacetic acid* (3·2 g.), m. p. 50°. The residual oily precipitate crystallised on trituration under water; recrystallization from ethyl acetate–light petroleum (b. p. 40—60°) gave a further 2·7 g., m. p. 50°, of the 2-methylthio-derivative (total yield : 5·9 g., 62%) (Found : C, 43·0; H, 5·7; N, 10·2. $C_{10}H_{16}O_3N_2S_2$ requires C, 43·1; H, 5·8; N, 10·1%). The 2-methylthio-derivative (3 g.) was suspended in ether (10 c.c.), and methylated with diazomethane (0·7 g.) in ether (50 c.c.). After 5 minutes the solution was evaporated to a colourless oil, which was reduced in ethanol (50 c.c.) with amalgamated aluminium foil (2 g.). The reaction mixture was filtered hot, and the alumina extracted with boiling ethanol (2 × 50 c.c.). Evaporation of the filtrates gave a colourless oil which was taken up in ether (20 c.c.) and kept at 0° for 16 hours, while *methyl 5-isopropylthiazolidine-4-carboxyamidoacetate* (0·8 g.), m. p. 84°, separated. The ethereal filtrate was largely diluted with light petroleum (b. p. 40—60°), giving rosettes of colourless needles, m. p. and mixed m. p. 80—82°. The peptide crystallised from a little hot water in colourless needles having m. p. 85° (Found : C, 49·0; H, 7·3; N, 11·5. $C_{10}H_{18}O_3N_2S$ requires C, 48·8; H, 7·4; N, 11·5%).

Reaction between 2-Mercapto-4-benzylidene-5-thiazolinone and Aminoacetamide.—A suspension of the thiazolinone (4·4 g.) in methanol (100 c.c.) containing N-sodium hydroxide (20 c.c.) and aminoacetamide hydrochloride (2·3 g.) was heated under reflux for 1 hour, diluted with water (200 c.c.), and cooled. The pale yellow solid product (2 g.), m. p. 220°, was recrystallized from the minimum quantity of hot glacial acetic acid, whereupon *2-thio-4-benzylidenehydantoin-1-acetamide* (1·3 g.), m. p. 257°, separated. For analysis, a small quantity was recrystallized from much hot water, forming long pale yellow needles, m. p. 257° (Found : C, 55·4; H, 4·3; N, 16·0. $C_{12}H_{11}O_2N_3S$ requires C, 55·2; H, 4·3; N, 16·1%).

The amide (1 g.) treated in a solution of potassium hydroxide (0·19 g.) in water (10 c.c.) with methyl sulphate (0·3 c.c.) gave a rapidly-crystallizing oil. *2-Methylthio-5-keto-4-benzylidene-4 : 5-dihydroglyoxaline-1-acetamide* (0·7 g.) was filtered off. It separated from aqueous methanol as pale yellow rhombohedra, m. p. 154° (Found : C, 56·9; H, 5·2; N, 15·3. $C_{13}H_{13}O_2N_3S$ requires C, 56·7; H, 5·5; N, 15·2%).

The acetic acid solution from crystallization of the thiohydantoin was largely diluted with water, whereby further material (0·5 g.) m. p. 190—193°, was precipitated. This was recrystallized from hot water, giving *2-mercapto-5-phenylthiazoline-4-carboxyamidoacetamide* as colourless rods, m. p. 200° (Found : N, 14·1. $C_{12}H_{12}O_2N_3S_2$ requires N, 14·2%).

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388. *Characterisation of* 3 : 4-*Dimethyl* D-*Glucose.*

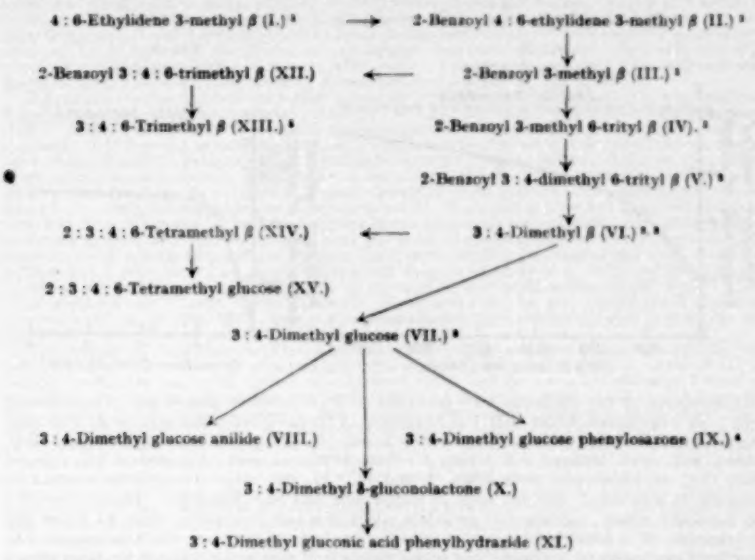
By D. J. BELL and G. D. GREVILLE.

3 : 4-Dimethyl D-glucose, first described by Dewar and Fort (*J.*, 1944, 496), has been synthesised by a somewhat different route and its constitution proved by (*a*) formation of a crystalline phenylosazone containing two methoxyl groups, (*b*) oxidation to the corresponding δ-lactone, characterised as the crystalline 3 : 4-dimethyl gluconic acid phenylhydrazide, and (*c*) periodate oxidation. During this oxidation the 1 : 2-link is attacked rapidly, yielding formic acid, and thereafter a slow production of formaldehyde ensues, presumably by fission of the 5 : 6-link. The sugar itself is most readily characterised as the crystalline anilide. The polarimetric behaviour of the sugar has been described incorrectly by Dewar and Fort.

SEVERAL years ago we started work on the synthesis of 3 : 4-dimethyl D-glucose, at that time unknown. We intended to attempt this through a partial acetolytic opening of the dioxan ring of 4 : 6-ethylidene 3-methyl β-methylglucoside (cf. Bell and Synge, *J.*, 1937, 1711), but, although crystalline compounds were obtained at various later stages, these did not appear to have the desired structures, and the attempt was abandoned. Subsequently Dewar and Fort (*J.*, 1944, 496) described the synthesis of crystalline 3 : 4-dimethyl glucose starting with 4 : 6-ethylidene β-methylglucoside 2 : 3-dinitrate. These authors, likewise, encountered difficulty when attempting partial acetolysis of the ethylidene radical in their substances. Later work in this laboratory, however, rendered imperative the preparation of a quantity of

3 : 4-dimethyl glucose; we therefore recommenced our own work and, since Dewar and Fort gave no proof of the constitution of their sugar beyond that provided by their method of synthesis, we decided to characterise the sugar more fully.

The synthetic route adopted followed closely in its later stages that of Dewar and Fort. Certain improvements were introduced, notably (1) the use of the crystalline chloroform addition compound of 3-methyl β-methylglucoside as starting material for the preparation of its 4 : 6-ethylidene derivative (I), (2) the use of toluene during the working-up of the trityl compound (IV), and (3) the adoption of a totally different procedure for passing from (V) to (VI) (see following scheme, in which " β " denotes β-methylglucoside).


4 : 6-Ethylidene 3-methyl β (I.) [1]
2-Benzoyl 4 : 6-ethylidene 3-methyl β (II.) [1]
2-Benzoyl 3 : 4 : 6-trimethyl β (XII.)
2-Benzoyl 3-methyl β (III.) [1]
3 : 4 : 6-Trimethyl β (XIII.) [1]
2-Benzoyl 3-methyl 6-trityl β (IV). [1]
2-Benzoyl 3 : 4-dimethyl 6-trityl β (V.) [1]
2 : 3 : 4 : 6-Tetramethyl β (XIV.)
3 : 4-Dimethyl β (VI.) [1] [2]
2 : 3 : 4 : 6-Tetramethyl glucose (XV.)
3 : 4-Dimethyl glucose (VII.) [2]
3 : 4-Dimethyl glucose anilide (VIII.)
3 : 4-Dimethyl glucose phenylosazone (IX.) [4]
3 : 4-Dimethyl δ-gluconolactone (X.)
3 : 4-Dimethyl gluconic acid phenylhydrazide (XI.)

[1] Reeves, *J. Amer. Chem. Soc.*, 1944, **66**, 845. [2] Dewar and Fort, *loc. cit.* [3] Dewar, Fort and McArthur, *J.*, 1944, 499. [4] McDonald and Jackson, *Bur. Stand. J. Res.*, 1940, **24**, 181. [5] Haworth, Hirst, and Panizzon, *J.*, 1934, 154; Sundberg, McClosky, Rees, and Coleman, *J. Amer. Chem. Soc.*, 1945, **67**, 1080.

It may be noted that the benzoyl radical occupying position 2 in (III) and (IV) does not migrate when these compounds are treated with Purdie's reagents; from (III), crystalline 3 : 4 : 6-trimethyl β-methylglucoside was obtained in good yield (this will be the subject of a future note with Dr. D. H. Northcote).

When we examined our specimen of crystalline 3 : 4-dimethyl glucose we found that, although it had the melting point recorded by Dewar and Fort, it showed very different polarimetric behaviour. Through the kind co-operation of Dr. J. Dewar we were able to re-examine the rotation of his original specimen; we find that it is indeed identical with our material. It is therefore clear that Dewar and Fort misquoted the polarimetric values, and also the direction of the mutarotation, in their report (see below).

Specific rotations of samples of 3 : 4-*dimethyl* D-*glucose.*

Source of sample.	$[\alpha]_D$ in water.	$[\alpha]_D$ in methanol.
Present authors	+93·5° (2·5 mins.) ⟶ +77·8° (9·5 hrs., equilibrium)	+96·1° (1 min.) ⟶ +92·1° (6·8 hrs., equilibrium)
Dewar and Fort (by present authors)	+76·6° (3 mins.) ⟶ +76·6° (15 hrs.)	+97·6° (4 mins.) ⟶ +92·0° (10 mins., equilibrium)
Dewar and Fort (published values)	+64·9° (10 mins.) ⟶ +94·8° (24 hrs.)	+88·5° (6 mins.) ⟶ +102·2° (24 hrs.)

From the downward trend of the mutarotation it may be deduced that the crystalline sugar contains a preponderance of the α-anomer.

A convenient derivative for the identification of 3 : 4-dimethyl glucose is the crystalline anilide, which we have obtained in good yield. The phenylosazone can also be prepared; it was obtained in easily crystallisable form by seeding with material prepared from synthetic 3 : 4-dimethyl D-fructose and kindly provided by Dr. Emma J. McDonald of the U.S. Bureau of Standards.

Oxidation of the sugar with bromine water, followed by appropriate treatment, yielded a syrupy δ-lactone which, however, yields a readily crystallisable phenylhydrazide.

Oxidation of 3 : 4-*dimethyl glucose by periodate in phosphate buffer* (pH 7·4).

FIG. 1.

4·1 *Moles of periodate.*

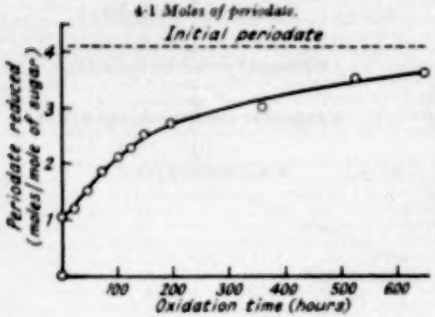
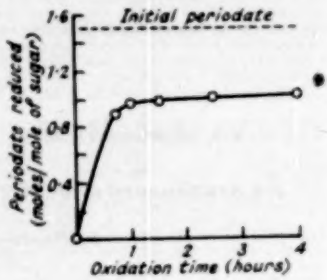


FIG. 2.

1·5 *Moles of periodate.*



Experiments on the oxidation with periodate of 3 : 4-dimethyl glucose gave the following results : In bicarbonate buffer (pH 7·5) formation of formaldehyde was very slow, 0·55 mole being produced from one mole of sugar in 860 hours. In phosphate buffer (pH 7·4) (cf. Bell, *J.*, 1948, 992; Bell, Palmer, and Johns, *J.*, 1949, 1536) one mole of periodate was reduced rapidly, *i.e.*, in about one hour (Figs. 1 and 2). At this stage a negligible amount of formaldehyde was found, but one mole of formic acid had been liberated. There followed a slow, but fairly steady, reduction of periodate which was still proceeding when 3·5 moles had been reduced. 3 : 4-Dimethyl glucose, reacting in the open-chain form, would be expected to reduce only two moles of periodate, but it has been found that some other methylated sugars reduce more than the expected amount of periodate in phosphate buffer (Bell, Palmer, and Johns, *loc. cit.*). At 216 hours when 2·96 moles of periodate had been reduced, one mole of sugar had produced 0·84 mole of formaldehyde. With this sugar, therefore, periodate first attacks the 1 : 2-link yielding formic acid, and subsequently causes a slow production of formaldehyde, presumably by fission of the 5 : 6-link.

The constitution of the sugar was confirmed by the following : (1) Complete methylation of the glucoside (VI) yielded crystalline 2 : 3 : 4 : 6-tetramethyl β-methylglucoside, which on hydrolysis gave 2 : 3 : 4 : 6-tetramethyl glucose. (2) The formation of formic acid and formaldehyde by periodate oxidation is consistent with etherification in positions 3 and 4. (3) The sugar yields a dimethyl glucose phenylosazone, which is identical with that from 3 : 4-dimethyl fructose. (4) The lactone obtained after bromine oxidation behaves in solution as a member of the δ-series, confirming substitution of the hydroxyl group of position 4.

EXPERIMENTAL.

M. p.s are uncorrected unless otherwise stated. Rotations were measured in 2-dm. tubes. Solvents were removed under reduced pressure, and solvents distilled in glass were used for crystallisations. Elementary analyses were by Drs. Weiler and Strauss, Oxford.

4 : 6-*Ethylidene* 3-*Methyl* β-*Methylglucoside* (I).—The crystalline chloroform addition compound of 3-methyl β-methylglucoside (Oldham, *J. Amer. Chem. Soc.*, 1934, **56**, 1360) was dried to constant weight over calcium chloride in a desiccator continuously evacuated at *ca.* 15 mm. (4·5 hours). The product (21 g., equivalent to *ca.* 13 g. of the glucoside) was then shaken vigorously with 150 ml. of freshly-distilled paraldehyde containing 1% (v/v) of concentrated sulphuric acid and previously cooled to *ca.* 10°. After the mixture had been kept at 4°, and shaken at intervals, for 30 minutes most of the solid had dissolved.

The fluid was decanted into 200 ml. of 7·5% potassium carbonate solution, and the undissolved residue treated with a further 30 ml. of the paraldehyde–sulphuric acid mixture, dissolving completely in 15 minutes. The resulting fluid was then added to the potassium carbonate solution. The whole was then distilled under reduced pressure to remove unchanged paraldehyde, and the aqueous solution remaining was extracted 3 times with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated, leaving a crystalline residue (16 g.) which after recrystallisation from ethanol–light petroleum (b. p. 40—60°) yielded (I) (11 g.), m. p. 133—134°, $[\alpha]_D^{18}$ −43·5° in chloroform (*c*, 4·6). Dewar and Fort (*loc. cit.*) give m. p. 134°, $[\alpha]_D^{18}$ −43·7° in chloroform; Reeves (*loc. cit.*) gives m. p. 133—134° (corr.). The residues from the recrystallisation yielded a crystalline substance, m. p. 96°, soluble in light petroleum (b. p. 40—60°), which has not yet been identified.

2-*Benzoyl* 4 : 6-*Ethylidene* 3-*Methyl* β-*Methylglucoside* (II).—The substance (I) (dried over phosphoric oxide) was dissolved with gentle warming in dry pyridine (4 moles); benzoyl chloride (2·3 moles) was added, the mixture being cooled in ice. Not more than 10 g. of the glucoside were treated at a time. After being kept at room temperature for 24 hours the mixture was stirred with water; 3 hours later the solid which had separated was filtered off and washed, first with much water, then with very dilute ammonia solution, and finally once more with water. Recrystallisation from 4 : 1 methanol–water gave (II), m. p. 157—159°, in 90% yield. Dewar and Fort (*loc. cit.*) give m. p. 159°.

2-*Benzoyl* 3 : 4-*Dimethyl* 6-*Trityl* β-*Methylglucoside* (V).—The above compound (II) was hydrolysed, following the instructions of Dewar and Fort (*loc. cit.*), to give 2-benzoyl 3-methyl β-methylglucoside (III), m. p. 139—140° (from carbon tetrachloride–chloroform). Dewar and Fort give m. p. 142—143°. The compound (III) (8·45 g.; dried in high vacuum) was heated, for 3 hours at 100° (air-bath temperature), with triphenylmethyl chloride (7·35 g., 0·975 mole) and dry pyridine (42 ml.) under an air-condenser fitted with a calcium chloride guard-tube. After cooling, the mixture was diluted with 250 ml. of toluene (chosen because the partition coefficient toluene/water for pyridine is low), and the whole poured into 4 l. of a 0·25% sodium hydrogen carbonate solution. The aqueous layer was separated and shaken with a little more toluene. The united toluene layers were again washed, first with sodium hydrogen carbonate solution and then with water, until the smell of pyridine was scarcely perceptible. After treatment with sodium sulphate and charcoal the toluene solution was filtered and evaporated. The residue (IV), a pale yellow glass, was dried in a high vacuum (yield, 14·35 g., 96%) and had $[\alpha]_D^{18}$ −9·1° in chloroform (*c*, 4·1). Dewar and Fort (*loc. cit.*) give $[\alpha]_D^{18}$ −8·9° in chloroform, yield 79%.

Methylation of (IV) with Purdie's reagents (Dewar and Fort, *loc. cit.*) yielded the 3 : 4-dimethyl derivative (V), m. p. 138—139°. Repeated recrystallisation from methanol failed to raise the m. p. above 139—140°. Dewar and Fort (*loc. cit.*) give m. p. 142°.

3 : 4-*Dimethyl* β-*Methylglucoside* (VI).—The compound (V) (8·0 g.) was dissolved in ethanol (36 ml.) under reflux and 35 ml. of 0·85*N*-aqueous sodium hydroxide (*ca.* 100% excess) added slowly. After 30 minutes' boiling the solution was cooled, 300 ml. of water were added, and the whole was extracted 3 times with chloroform. The combined extracts were washed with a little water, dried (Na_2SO_4), and evaporated. The resulting de-benzoylated product, a glass, was then heated under reflux with 90 ml. of acetone and 10 ml. of 0·1*N*-hydrochloric acid, the reaction being followed polarimetrically (7 hours). After cooling of the mixture more water was added, followed by an excess of silver carbonate. The solid material was removed by filtration (charcoal) and washed with water. The combined filtrate and washings were concentrated to remove acetone; trityl compounds which separated during this procedure were filtered off and washed with water. The filtrate and washings were combined and, after concentration, were extracted 3 times with benzene to complete the removal of trityl compounds. The aqueous solution was then evaporated, the residue dissolved in ethanol, and this solution filtered and evaporated below 50°. The product (VI) crystallised immediately when seeded; it weighed 2·70 g. after drying in a high vacuum. It was distilled at 0·05 mm. (bath-temperature *ca.* 150°) to give crystals, m. p. 80—83°, $[\alpha]_D^{18}$ −12·3° in chloroform (*c*, 5·1) [2·40 g., 77% from (V)]. Dewar and Fort (*loc. cit.*) give m. p. 79—81°, $[\alpha]_D^{18}$ −11·9° in chloroform, after recrystallisation.

2 : 3 : 4 : 6-*Tetramethyl* D-*Glucose* (XV) *from* (VI).—The glucoside (VI) (0·299 g.) was twice methylated with Purdie's reagents. The product crystallised, and after drying over sulphuric acid and solid sodium hydroxide at atmospheric pressure (the substance is volatile under reduced pressure at room temperature) weighed 0·33 g. (yield approx. theoretical) and had $[\alpha]_D^{18}$ −17·3° in water (*c*, 4·7). Irvine and Cameron (*J.*, 1905, **87**, 900) give $[\alpha]_D^{20}$ −17·3° in water.

The crystals (0·2 g.) were hydrolysed by heating with *N*-hydrochloric acid at 95—100° for 5·5 hours. After appropriate treatment the hydrolysate yielded 0·15 g. of crystalline material. This was recrystallised from light petroleum (b. p. 40—60°), yielding 0·069 g. of 2 : 3 : 4 : 6-tetramethyl glucose, m. p. 86—92°, not depressed on admixture with authentic material of m. p. 90—92°, and having $[\alpha]_D^{18}$ +82·4° in water (*c*, 2·05) at equilibrium. Haworth, Long, and Plant (*J.*, 1927, 2809) give $[\alpha]_D^{18}$ +83·0°. The mother-liquors from the recrystallisation were evaporated, leaving a crystalline residue. On a paper chromatogram (*n*-butanol–water) this residue gave only one spot. R_F values were: recrystallised material, 79·5; residue 79; authentic material 79·5.

3 : 4-*Dimethyl Glucose* (VII).—The glucoside (VI) was hydrolysed in 5% solution in *N*-hydrochloric acid at 95—100°, the reaction being followed polarimetrically (5·5 hours). The solution was treated with a small excess of silver carbonate and filtered (charcoal–"Celite") before and after passage of hydrogen sulphide. The solution was then evaporated below 50°, and the residue dissolved in ethanol, filtered, and evaporated. Two recrystallisations of the residue from dry ethyl acetate yielded (VII), m. p. 110—113°. Dewar and Fort (*loc. cit.*) give 113°. The m. p. was not depressed on admixture with a specimen (m. p. 110—112°) from Dr. Dewar. The sugar was dried to constant weight in a high vacuum at room temperature (Found: C, 46·2; H, 7·55. Calc. for $C_8H_{16}O_6$: C, 46·2; H, 7·7%). For rotation, see Table (p. 1903). Dr. Dewar's specimen contained a small amount of an impurity insoluble in propyl acetate, and after recrystallisation from this solvent had $[\alpha]_D^{18}$ in methanol (*c*, 0·45) +97·6° (4 minutes), +92·0° (10 minutes, equilibrium value).

Our material gave a single compact spot on a paper chromatogram (*n*-butanol–water or ethyl acetate–water).

3 : 4-*Dimethyl Glucose Anilide* (VIII).—The sugar (VII), in 5% solution in dry ethanol, was refluxed with aniline (1·5 moles) for 5 hours. Evaporation of the solvent and recrystallisation of the residue, first from *n*-butanol–light petroleum (b. p. 40—60°), then from ethanol, gave the ***anilide*** (VIII) as colourless needles, m. p. 177—178° (not raised by further recrystallisation from ethanol), $[\alpha]_D^{20}$ in ethanol (*c*, 2·2) −106° (17 minutes), −106° (17 hours) (Found: C, 59·2; H, 7·5; N, 4·85; OMe, 21·4. $C_{14}H_{21}O_5N$ requires C, 59·4; H, 7·4; N, 4·95; OMe, 21·9%).

3 : 4-*Dimethyl Glucose Phenylosazone* (IX).—A solution of the sugar (VII) in dilute acetic acid was heated for 75 minutes at 100° with phenylhydrazine (*ca.* 4·5 moles) and a little sodium hydrogen sulphite (Hamilton, *J. Amer. Chem. Soc.*, 1934, **56**, 487). The oil which separated crystallised when seeded with the phenylosazone from 3 : 4-dimethyl fructose, kindly supplied by Dr. Emma J. McDonald. The crystals were washed thoroughly with water and dried in a high vacuum over phosphoric oxide. After two recrystallisations (charcoal) from ether–light petroleum (b. p. 60—80°) the yellow needles (IX) had m. p. 126—127° (Found: C, 62·2; H, 6·9; N, 14·6; OMe, 16·4. Calc. for $C_{28}H_{32}O_4N_4$: C, 62·2; H, 6·75; N, 14·5; OMe, 16·1%). Another preparation had m. p. 120°, unchanged by further recrystallisation. It is noteworthy that the phenylosazone from 3 : 4-dimethyl fructose (obtained from irisin; forthcoming communication), which showed no depression of m. p. on being mixed with (IX), melted at 126°, but had m. p. 120° after further recrystallisation. McDonald and Jackson (*loc. cit.*) obtained two specimens of the phenylosazone from synthetic 3 : 4-dimethyl fructose with m. p. 126° and a third with m. p. 121° (no analyses given). Haworth, Hirst, and Isherwood (*J.*, 1937, 784) prepared the phenylosazone from 3 : 4-dimethyl mannose but were unable to determine a m. p.

3 : 4-*Dimethyl* δ-*Gluconolactone* (X).—The sugar (VII), in 5% solution in water, was oxidised by bromine at room temperature, a small amount of undissolved bromine being kept present throughout. After 30 hours Fehling's test was negative. The solution was then neutralised with a slight excess of silver carbonate (free from alkali and alkaline-earth metals) and filtered (charcoal–"Celite") before and after hydrogen sulphide had been passed in. It was evaporated, leaving a syrupy residue which was distilled at 0·01 mm. (bath-temperature *ca.* 150°; receiving surface cooled with acetone–carbon dioxide), yielding 3 : 4-*dimethyl gluconolactone* (X) as a colourless syrup (Found: OMe, 29·85. $C_8H_{14}O_6$ requires OMe, 30·1%), n_D^{20} 1·4862 (decrement for rise of 1°, 0·00028 from 19° to 29°), $[\alpha]_D^{20}$ in water (*c*, 1·2) +70·8° (9 minutes), +57·2° (70 minutes), +30·5° (220 minutes), +20·2° (350 minutes), +16·4° (10·5 hours), +16·0° (22 hours, equilibrium value). The rate of hydrolysis indicates a δ-lactone.

3 : 4-*Dimethyl Gluconic Acid Phenylhydrazide* (XI).—The lactone (X) (0·33 g.) was dissolved under reflux in dry benzene (9 ml.) with the aid of a few drops of absolute ethanol. Phenylhydrazine (0·28 ml., *ca.* 2 moles) was added and the solution boiled for 5 hours. It was then evaporated; the residue crystallised on being warmed with dry ether. The crystals were washed with small quantities of dry ether and of ether–light petroleum (b. p. 80—100°). Recrystallisation from ethanol–ether–light petroleum (b. p. 80—100°) gave the ***phenylhydrazide*** (XI) as colourless needles, m. p. 119° (not raised by further recrystallisation) (0·33 g., 66%), $[\alpha]_D^{20}$ +27·1° in ethanol (*c*, 1·6) (Found: C, 53·55; H, 7·0; N, 9·45; OMe, 20·1. $C_{14}H_{22}O_5N_2$ requires C, 53·5; H, 7·0; N, 8·9; OMe, 19·7%).

Oxidation of 3 : 4-*Dimethyl Glucose by Periodate.*—The oxidations were done at room temperature. The amounts of periodate reduced, and of formaldehyde and formic acid formed, are expressed as moles (or g.-equivs.) per mole of sugar initially present. Simultaneous control determinations on the reagents were always carried out and the necessary slight corrections made.

(a) *In bicarbonate buffer.* The formaldehyde formed when the sugar, in 9mM-solution, was treated with periodate (6·7 moles) in bicarbonate buffer (pH 7·5) was determined according to Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476). Formaldehyde was produced very slowly. The formaldehyde-dimedon compound had m. p. 193° (corr.).

Oxidation time (hrs.)	22	96	860
Formaldehyde produced (moles per mole)	0·09	0·24	0·55

(b) *In phosphate buffer.* Periodate was determined by titration of samples of the reaction mixture with 0·02N-sodium arsenite after addition of water and potassium iodide. In the experiment shown in Fig. 1 the sugar, in 4mM-solution, was oxidised with periodate (4·1 moles) in 0·025M-sodium phosphate at pH 7·4. 1·07 Moles of periodate were reduced in the first 2·5 hours; thereafter there was a slow but fairly steady reduction, still proceeding at 600 hours. The initial rapid reduction was examined more closely in another experiment (Fig. 2) in which the sugar, in 15mM-solution, was treated with 1·5 moles of periodate; 1 mole of periodate was reduced in about 1 hour.

Formaldehyde production was studied as follows: The sugar, in 6mM-solution, was oxidised with periodate (3·4 moles) in 0·03M-sodium phosphate at pH 7·4. Samples (10 ml.) were removed at intervals and treated with N-hydrochloric acid (3 ml.) and 1·2M-potassium arsenite (B.D.H.) (1 ml.). When the liberated iodine had disappeared, bromocresol-green was added, followed by M-sodium acetate until the solution was blue-green. The formaldehyde was then determined by weighing the dimedon compound, m. p. 188—189° (corr.), as described by Bell (*loc. cit.*). The results are given below. It is seen that the

Oxidation time (hrs.)	2	95	216
Periodate reduced (moles per mole)	1·05	2·28	2·96
Formaldehyde produced (mole per mole)	0·005	0·64	0·84

initial reduction of 1 mole of periodate is accompanied by negligible production of formaldehyde, but that during the subsequent reduction of more than the expected amount of periodate formaldehyde is slowly released.

Production of formic acid during the first few hours was determined as follows (cf. Bell, Palmer, and Johns, *loc. cit.*). The sugar, in 16mM-solution, was oxidised with periodate (1·48 moles) in 0·03M-phosphate at pH 7·5. Samples (2 ml.) of the reaction mixture were withdrawn at intervals, treated with purified ethylene glycol (0·5 ml.) and after 1 hour diluted to 10 ml. with 10% potassium hydrogen sulphate. Samples (3 ml.) of this solution were then pipetted into the steam-distillation

apparatus (Markham, *Biochem. J.*, 1942, **36**, 790); 65 ml. of distillate were collected and titrated with 0·01N-sodium hydroxide (carbon dioxide-free) in a stream of carbon dioxide-free air, with phenol-red as indicator. The blank determination on the reagents was 0·015 ml. of sodium hydroxide, corresponding to 0·02 g.-equiv. of volatile acid per mole of sugar. Distillations were run in duplicate. Control determinations on formic acid put through the whole process showed a recovery of approx. 99%. The results are given below.

Oxidation time (mins.)	45	75	240
Periodate reduced (moles per mole)	0·99	1·02	1·07
Volatile acid formed (g.-equivs. per mole)	0·94	0·99	1·01

Evidence that the volatile acid was in fact formic acid was obtained as follows: The distillates, made slightly alkaline with sodium hydroxide, were evaporated (Pirie, *Biochem. J.*, 1946, **40**, 100) and the residues heated in glass-stoppered tubes with 2 ml. of 5% mercuric sulphate in 0·5*N*-sulphuric acid for 1 hour at 100°. The resulting suspensions were distilled and titrated as before. Alternatively, the dried residues were dissolved in 3 ml. of the acid mercuric sulphate solution and distilled, slowly at first, without preliminary heating. Both methods resulted in quantitative elimination of the volatile acid.

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389. *Oxidations with Sodium Bismuthate: Glycol Fission and Related Reactions.*

By W. RIGBY.

Sodium bismuthate in an acid medium smoothly and selectively effects oxidations similar to those brought about by lead tetra-acetate and periodic acid; αβ-glycols undergo fission to aldehydes or ketones, acyloins to the derived carbonyl compound and carboxylic acid, and α-hydroxy-acids to the lower aldehyde or ketone, all in good yield. Aldehydes are not further oxidised.

Of the relatively small number of reagents which effect the scission of αβ-glycols, converting the >C(OH)·C(OH)< group into >CO and OC<, only two—periodic acid (Malaprade, *Bull. Soc. chim.*, 1928, **43**, 683; *Compt. rend.*, 1931, **186**, 382) and lead tetra-acetate (Criegee, *Ber.*, 1931, **64**, 260)—have found wide application. Closely related reactions—scission of >C(OH)·CO⁻ to >CO + HO·CO⁻, degradation of α-hydroxy-acids to the corresponding carbonyl compound, and some ammono-analogues of these reactions—are also brought about, the differences between the two reagents in this respect being of degree rather than of kind, and the reagents are reasonably specific for these types of oxidation. In practice, periodate and lead tetra-acetate are more or less complementary, the former having perhaps its greatest value in quantitative applications and in reactions requiring the use of aqueous media, while the latter is not so well suited for quantitative work and is typically used in non-aqueous media for preparative purposes. Other reagents capable of effecting selective oxidative glycol cleavage are known (cf. Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159) but have been less investigated or have been shown to be less convenient for general use; some of the more familiar oxidising agents can also be shown to be capable of producing the typical "glycol fission" products, but they either lack selectivity or bring about the result by a more or less minor side reaction; Slack and Waters (*J.*, 1949, 594) have shown that the same cleavage products represent a stage in the oxidation of αβ-glycols by chromyl chloride.

Compounds of bismuth have been but little investigated as oxidising agents for organic compounds, but from the broad analogies subsisting between lead and bismuth, and especially from the occurrence in both of valency states of high oxidising potential two units above the common state, oxidations by quinquevalent bismuth might be expected to be analogous to those by quadrivalent lead. Experiment confirmed this, as was announced in a preliminary note (Rigby, *Nature*, 1949, **164**, 185). Sodium bismuthate is available commercially, is quite stable, can be used directly, and in an acid medium at or about room temperature rapidly effects typical glycol fissions. The course of the reaction is readily followed visually, the carbonyl compounds are produced in good yield, and there appears to be no tendency for aldehydes to be oxidised further. The rates of reaction are comparable with those of the corresponding periodate and lead tetra-acetate oxidations. The oxidation can be carried out in water, an organic solvent, or mixtures of the two, bismuthate having the advantage over lead tetra-acetate in this respect (Criegee and Büchner, *Ber.*, 1940, **73**, 563). Like lead tetra-acetate, and unlike periodate, sodium bismuthate rapidly and smoothly oxidises α-hydroxy-acids to the lower aldehyde or ketone. Methyl and ethyl alcohols are only slowly oxidised, even when present in high concentration but, in contrast with Malaprade's reagent, bismuthate rapidly oxidises formic acid and,

less rapidly, oxalic acid. While aldehydes in general are unattacked, a 10% aqueous solution of technical glyoxal was rapidly oxidised. With the only pair of *cis–trans*-glycols tried, the *cyclo*hexane-1 : 2-diols, no notable difference in rate of reaction with bismuthate was observed.

Two general experimental procedures have been used. In the first, the sodium bismuthate (usually the theoretical amount) is stirred or shaken with a solution of the glycol in glacial acetic acid at, or slightly above, room temperature until the reddish-brown, finely suspended bismuth pentoxide disappears and a clear colourless solution results (this requires a few minutes to several hours); if desired, the bismuth can be completely removed from the resulting solution by precipitation as phosphate. The marked change in appearance during reaction makes this procedure a convenient qualitative test for the classes of substances oxidised by the reagent. In the second procedure, the reaction is similarly carried out in water or aqueous dioxan in the presence of a slight excess of phosphoric acid. The initial bright orange-yellow suspension (presumably some compound of bismuth pentoxide and phosphoric acid) is ultimately replaced by pure white bismuth phosphate, again making it easy to follow the reaction visually. When the reaction products are isolated by ether-extraction, there is usually no need to filter off the bismuth phosphate, as it does not interfere or cause emulsification.

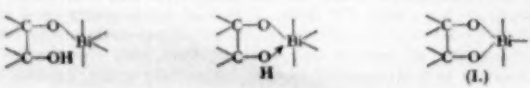
On a 1/50—1/200-mol. scale, the expected products (given in parentheses) were isolated as derivatives from the following: ethylene glycol (formaldehyde); glycerol 1-benzyl ether (benzyloxyacetaldehyde); ethyl tartrate (ethyl glyoxylate); *cis-* and *trans-cyclo*hexane-1 : 2-diol (adipdialdehyde); *trans*-tetralin-1 : 2-diol (*o*-2-formylethylbenzaldehyde); *threo*-9 : 10-dihydroxystearic acid (pelargonaldehyde and azelaic acid-aldehyde); hydrobenzoin (benzaldehyde); pinacol hydrate (acetone); glycerol (formaldehyde and glycollaldehyde); benzoin (benzaldehyde and benzoic acid); 4-methoxybenzoin (benzaldehyde and *p*-anisic acid); lactic acid (acetaldehyde); mandelic acid (benzaldehyde); α-hydroxy*iso*butyric acid (acetone); and benzilic acid (benzophenone).

Moderate-scale preparations have been developed for: ethyl glyoxylate alcoholate (51%); adipdialdehyde (49% from *trans-cyclo*hexane-1 : 2-diol; cf. Criegee, *loc. cit.*, 67% from the *cis*-diol, and Engliah and Barber, *J. Amer. Chem. Soc.*, **1949**, **71**, 3310, 68% from mixed *cis-trans*-diols, both by means of lead tetra-acetate), and its cyclic monoacetal with *cis-cyclo*hexane-1 : 2-diol (33% from *cis-cyclo*hexane-1 : 2-diol); benzyloxyacetaldehyde (68%), pelargonaldehyde [53%; isolation of azelaic acid-aldehyde in a pure state from the same reaction being unsatisfactory (17%)].

Glycollaldehyde and formaldehyde (formed together by the oxidation of glycerol) are readily separated as dimedon derivatives by making use of the solubility of the formaldehyde–dimedon compound in benzene and that of the glycollaldehyde derivative in 60% alcohol. The product from glycollaldehyde is an anhydro-compound; whether it has a xanthan structure has not been determined.

Simple methods have been evolved for the preparation of *cis-* (*ca.* 36% yield), and *trans-cyclo*hexane-1 : 2-diol (*ca.* 50% yield).

The mechanism of the reaction of bismuthate with glycols is presumably essentially similar to those of oxidation with lead tetra-acetate of periodic acid, concerning which however there is still controversy. Many examples are known or organic compounds which contain adjacent hydroxyl groups reacting readily with metal hydroxides to produce substances considered to contain the group M or R–O–M, hydroxides of copper, iron, aluminium, bismuth^{III}, boron, etc., being typical. Criegee and Büchner (*loc. cit.*) considered that $Pb(OAc)_2(OH)_2$ must react with glycols in this sort of way more readily than does the tetra-acetate in order to account for the catalytic effect of water on the lead tetra-acetate oxidation. The metals and their valency states are diverse enough to make it reasonable to suppose that formation of such metal derivatives is a general property, and that the specific nature and valency of the metal are of secondary importance—with the obvious reservation that they should not favour ionic structures to the exclusion of covalent ones. If so, hydrated bismuth pentoxide might be expected to combine with a suitable polyhydroxy-compound in an analogous manner, at least as a primary act, and a theory of the mechanism of the oxidation reaction would then concern itself with transformations of the primary compound which would contain some such structure as



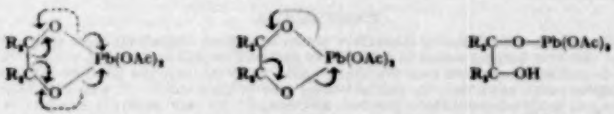
(I.)

The bismuth in such a compound is apparently able to withdraw permanently two electrons from the organic moiety and fission of a C–C bond results. Such a cyclic intermediate compound as (I) would be analogous to the lead compound (V) formerly postulated by Criegee (*loc. cit.*) as the immediate precursor of the fission reaction; an analogous stage has been assumed to account for the Malaprade reaction.

Dewar ("The Electronic Theory of Organic Chemistry," Oxford, 1949, pp. 276—277) formulates the lead tetra-acetate reaction as

and, from considerations of the bond-energies involved, gives a satisfying explanation of the resistance of ordinary alcohols to the reagent; he maintains that "The essential feature of the two reagents [Criegee's and Malaprade's] is their ability to accept simultaneously the two H atoms from the glycol."

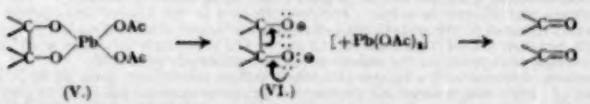
A formulation analogous to Dewar's would be better applied to Criegee's postulated cyclic intermediate; this would be (II), where also the passage of the two "reducing" electrons to the inner shell of the lead atom would be facilitated by the *simultaneous* withdrawal of the electrons from the C–C link. This is the essential feature of the process: the cyclic compound is a mechanism which allows the energy necessary to break the C–C bond to be, in part, provided by



(II.) (III.) (IV.)

that liberated on the formation of other bonds. Formally, the bond fissions need not be written as homolytic, formulation (III) giving the same result. Such a scheme would give a plausible indication why a few reagents—periodate, quadrivalent lead, and quinquevalent bismuth—should specifically effect glycol fissions smoothly and with remarkable freedom from side reactions: they all concern elements which (*a*) can reasonably be envisaged as capable of forming a preliminary compound R M with the glycol, and (*b*) exist in two stable oxidation states which are two valency units apart, the lower representing a substance which is not an oxidising agent under ordinary conditions (Pb^{II} or Bi^{III}) or which no longer fulfils condition (*a*) (the IO_3' ion).

This proposed formulation seems preferable to that of Criegee (*Annalen*, 1948, **560**, 132—133) which involves a zwitterion (VI), this being essentially a polar form of an olefin peroxide (moloxide) since from the moment of its formation it will presumably have a *cis*-configuration; the relationship of (VI) to (III) is obvious. Criegee's mechanism puts the glycol-fission reaction

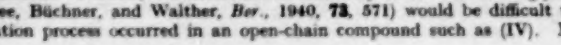


(V.) (VI.)

in line with certain others formulated by him as involving oxygen carrying a sextet of electrons and with reactions of C^+. In his discussion of the formation of ozonides, Criegee (*loc. cit.*, p. 131) points out that his proposed mechanism does not satisfactorily explain why the action of ozone on certain olefins does not lead to the formation of keto-hydroperoxides. Application of the same principles to a zwitterion (VI) derived from a non-tertiary glycol would similarly lead to the expectation of its transformation into an acyloin as an alternative to the observed "glycol-fission" products.

That a cyclic intermediate is an essential step in the lead tetra-acetate reaction has been demonstrated by Criegee: the specific effect of acetic acid in retarding the lead tetra-acetate oxidation is reasonably interpreted by him as being due to the primary formation of an open-chain compound (IV) which is stable to fission but cyclises to (V), and this then decomposes;

such an effect would not perhaps be explained so simply by using Dewar's bimolecular formulation. Further, the difference in reactivity of *cis*- and *trans*-glycols (Criegee, *loc. cit.*; Criegee, Büchner, and Walther, *Ber.*, 1940, **73**, 571) would be difficult to account for if the oxidation process occurred in an open-chain compound such as (IV). Mechanisms such as:



are therefore excluded. As soon, however, as the second hydroxyl group of the glycol became associated with the lead atom, the way would be open for the appropriate electron transfers to take place, and it is conceivable that they might occur practically simultaneously with ring closure and elimination of acetic acid.

As an explanation of any of these reactions, the two-stage free-radical mechanism proposed by Waters (*Trans. Faraday Soc.*, 1946, **42**, 184) seems less probable; Criegee and Büchner (*loc. cit.*, p. 566) have pointed out that the initial reaction with quadrivalent lead compounds cannot be a simple dehydrogenation, and Dewar (*loc. cit.*) has brought forward criticisms of Waters's mechanism for the lead tetra-acetate reaction which seem irrefutable. The difference in reactivity of *cis*- and *trans*-compounds is also a difficulty.

While the mechanism outlined here is suggested as being applicable in the cases defined, there is no reason to suppose that there can be only one path for the transition glycol ⟶ fission products, independently of the oxidising agent used, and it is reasonable to conclude with Waters (*Nature*, 1946, **158**, 380) that reaction of Fenton's reagent with pinacol to produce acetone involves free radicals.

Experimental.

Sodium Bismuthate.—Technical or laboratory grades of sodium bismuthate were used in the earlier experiments; different batches varied in colour from pale buff to pink and reddish-brown; dark grades appeared to be rather less reactive than the lighter ones. Only two samples failed to give a pure white bismuth phosphate after reduction, the product being grey in these cases. It was later found that the analytical-reagent grade offered definite practical advantages: its bulk density is about half that of the ordinary grade and it is free from grittiness. Although it is claimed (Scholder and Stobbe, *Z. anorg. Chem.*, 1941, **247**, 392) that it is possible to prepare sodium bismuthate of virtually 100% purity, commercially available material has an oxidising capacity equivalent to about 82—85% of $NaBiO_3$; very old samples which had suffered much exposure were no worse, and AnalaR samples had a titre of about 85%. The relatively few published methods for analysis of sodium bismuthate for available oxygen are not entirely satisfactory. A convenient method involves oxidation of Fe^{++}; this gives consistent results and is preferred for routine analysis; the results are reasonably close to those obtained gravimetrically by a process involving the oxidation of ethylene glycol to formaldehyde and weighing this as its dimedon derivative. Somewhat higher (2%) figures were obtained by a commercially-used iodometric assay, but, as no reasonable explanation offered itself for spuriously *low* results being obtained by the iron method, the fault probably lies with the iodometric method.

Analysis.—(*a*) *Preferred method.* The sample (0·45 g.) was swirled with ferrous sulphate solution (25 ml.; 0·125N. in 4N-sulphuric acid) and a dozen ¼" glass beads until dissolved, the beads breaking up any gritty particles. After addition of phosphoric acid (5—10 ml. of 85%) the solution was titrated with 0·1N-potassium dichromate (freshly prepared diphenylamine indicator). A blank determination was carried out.

(*b*) *Gravimetric method.* The sample (0·3—0·5 g.), in a 100-ml. graduated flask, was swirled with water (20 ml.), phosphoric acid (1 ml. of 3½N.), and ethylene glycol (0·04 mol.) until the solid became completely white (*ca.* 5—15 minutes), a known volume of glass beads being added if necessary. The mixture was diluted to volume and allowed to settle. Portions (25 ml.) of the filtered supernatant liquid were diluted to 50 ml., adjusted to pH *ca.* 4·5 with sodium acetate–acetic acid, and heated in the steam-bath for ½ hour with dimedon (0·2—0·3 g.) in alcohol (2 ml.). The precipitate was dried at 60° and weighed. The small correction was applied for the volume of bismuth phosphate produced.

Typical results, obtained with a sample of AnalaR sodium bismuthate, were (*a*) 85·1; (*b*) 86·1% of $NaBiO_3$. Bell (*J.*, 1948, 994) pointed out that certain grades of dimedon are liable to give high results in (semimicro-)formaldehyde determinations; no correction was applied in these bismuthate assays. A third analytical procedure, favoured by a commercial supplier of sodium bismuthate, involving liberation of iodine from potassium iodide in hydrochloric acid solution was found to give still higher results (*ca.* 87% of $NaBiO_3$ for the same sample).

Dioxan.—Technical material was purified (cf. Eigenberger, *J. prakt. Chem.*, 1931, [ii], **130**, 75) by being boiled for 7 hours with 10% of N-hydrochloric acid while acetaldehyde was removed by an air-stream; the product was dried (KOH) and distilled over sodium. Such material was inert to sodium bismuthate; technical dioxan reduced sodium bismuthate under the usual experimental conditions, giving rise to formaldehyde.

*cis-cyclo**Hexane*-1 : 2-*diol.*—*cyclo*Hexene (41 g.) was vigorously stirred under a reflux condenser with osmium tetroxide solution (5 ml. of 1%), and 100-volume hydrogen peroxide (60—65 ml.) was added very slowly (1 drop per 5 seconds) at 67°. After a short initial period when mixing was poor, the two phases formed a uniform emulsion under the vigorous stirring and the heat of reaction maintained the temperature; in some experiments a small amount of *cyclo*hexene remained undissolved at the end. Water was removed at reduced pressure and the residue distilled from an oil-bath. The material

(22 g.) distilling at 130°/25 mm. to 160°/4 mm. (mainly 130—140°/25 mm.) solidified, and on crystallisation from ethyl acetate or benzene gave the *cis*-diol, m. p. 97·5—99°.

trans-*cyclo*Hexane-1 : 2-*diol* (cf. Boesekan and Elsen, *Rec. Trav. chim.*, 1929, **48**, 369).—A solution of peracetic acid (*ca.* 1·3 mols.), made by heating acetic acid (480 ml.) and 100-volume hydrogen peroxide (150 g.) at 80—85° for 1 hour (Scanlan and Swern, *J. Amer. Chem. Soc.*, 1940, **62**, 2305), was added in 100-ml. portions to *cyclo*hexene (82 g.) stirred with occasional cooling as needed to keep the temperature at 45°. The addition required ½ hour, the *cyclo*hexene finally dissolving. After a further ½ hour at 45° the solution was heated in a boiling water-bath with a little spent palladium–charcoal catalyst until the perchromic acid test became negative. Water was distilled off, finally at 15—20 mm., alcohol (200 ml.) and hydrogen chloride (1—2 g.) or acetyl chloride (2—3 ml.) were added, and ethyl acetate and alcohol were slowly removed through a Vigreux column (b. p. *ca.* 74°). On distillation of the almost black crystalline residue, the fraction of b. p. 134—160°/15 mm. (mainly *ca.* 143°) was almost pure *trans*-diol. Recrystallisation from benzene or methyl ethyl ketone gave the pure material, m. p. 104·5—105·5° (63 and 37% in 2 experiments). The distillation residue yielded a *substance*, $C_{14}H_{22}O_4$, m. p. 193°, colourless prisms from technical 2-ethoxyethanol [Found : C, 70·0; H, 8·9%; *M* (Rast), 320. $C_{14}H_{22}O_4$ requires C, 70·1; H, 9·15%; *M*, 304).

trans-*Tetralin*-1 : 2-*diol*.—Crude dihydronaphthalene, b. p. 210·5—211·5°, prepared by reduction of naphthalene with sodium and alcohol, was oxidised with peracetic acid by a procedure analogous to that used in the case of *cyclo*hexene. After destruction of excess of peroxide by palladium–charcoal and removal of excess of acetic acid, the residue was heated for 1 hour with a slight excess of sodium hydroxide solution, to hydrolyse the ester, and the glycol was then extracted with ether. Removal of the ether and extraction of the residue with boiling water yielded almost pure *trans*-diol, which formed colourless needles, m. p. 112·5—113°, from water or ethyl acetate.

Oxidations.

Small-scale Experiments.—The glycol (0·01 mol.), AnalaR sodium bismuthate (0·01 mol. as determined by titration), 3½M-phosphoric acid (6—7 ml.), and water or dioxan (or both) (*ca.* 10—20 ml.) were shaken in 100-ml. stoppered bottles on a reciprocating machine until the bismuth compound was completely reduced (disappearance of the orange-yellow colour). If required, the bottles could be covered with layers of asbestos paper and heated to about 50° by radiation from an electric fire supported above the machine. The bismuth phosphate was removed by filtration, washed with water or alcohol, and, by treatment with the appropriate reagent, the carbonyl compound was isolated from the filtrate as a derivative which was recrystallised if necessary. In the following list, in parentheses after the name of the glycol, the solvent, the time for complete reduction, and the temperature are given.

Ethylene glycol [water (15 ml.), ¼ hour, room temperature] gave formaldehyde *p*-nitrophenylhydrazone, m. p. 178—179° (>90%), or the dimedon derivative, m. p. 189—190° after sintering at 185° (~100%). Glycerol 1-benzyl ether, b. p. 157·5°/3 mm. [water (15 ml.), ¼ hour, 20°], gave, after the oily aldehyde had been extracted with ether, *benzyloxyacetaldoxime* as colourless tablets (from light petroleum), m. p. 64—65° (Found : C, 65·4; H, 6·7; N, 8·65. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7; N, 8·5%). Ethyl tartrate [water (10 ml.), 3½ hours, 17—18°] gave glycollaldehyde phenylhydrazone, m. p. 128—129° (94%) (m. p. 131·5° after recrystallisation from methyl alcohol). *cis*- or *trans*-*cyclo*Hexane-1 : 2-diol [water (3 ml.) and purified dioxan (10 ml.), 2—3 hours at 30—40°, or 6 hours at 20—30°] gave adipic dialdehyde dioxime, m. p. 177—178° (70%). *trans*-Tetralin-1 : 2-diol, m. p. 113° [dioxan (15 ml.), 6 hours, 40°], gave o-2-*formylethylbenzaldehyde bis*-2 : 4-*dinitrophenylhydrazone*, small red lozenge-shaped crystals, m. p. 253° (decomp.) (unchanged on recrystallisation from cresol) (77%) (Found : C, 50·6; H, 3·8; N, 20·8. $C_{22}H_{18}N_8O_8$ requires C, 50·5; H, 3·5; N, 21·45); alternatively it gave the corresponding *bisphenylhydrazone*, m. p. 111°, pale buff prisms from alcohol (Found : C, 70·2; H, 5·9; N, 17·7. $C_{22}H_{22}N_4$ requires C, 77·1; H, 6·5; N, 16·4%). Pinacol hydrate [water (15 ml.), 3 hours, 30—40°] gave acetone 2 : 4-dinitrophenylhydrazone, m. p. 123—124° (99%), after separation of aqueous acetone from the reaction mixture by distillation. Hydrobenzoin, m. p. 138° [purified dioxan (15 ml.), 5½ hours, 40—50°], gave benzaldehyde phenylhydrazone, m. p. 158° (75%). Mandelic acid [water (25 ml.), 3½ hours, room temperature] gave benzaldehyde phenylhydrazone, m. p. 158° (64%). α-Hydroxy*iso*butyric acid [water (25 ml.), ¼—½ hour, room temperature] gave acetone 2 : 4-dinitrophenylhydrazone, m. p. 124—125° (82%), after separation of aqueous acetone from the reaction mixture by distillation. Benzilic acid [acetic acid (15 ml.) (phosphoric acid being omitted), 1½ hours, 50—60°] gave benzophenone, m. p. 49° (99%), isolated by ether extraction after addition of phosphoric acid (5 ml. of 3½M.).

A similar series of experiments was carried out by shaking the glycols (0·01 mol.) with sodium bismuthate (0·01 mol.) in glacial acetic acid (usually 15 ml.) until the reddish-brown suspension of bismuth pentoxide dissolved to give a clear solution; the bismuth was removed by precipitation with 5—6 ml. of 3½M-phosphoric acid, and the carbonyl compound isolated as a derivative. The results were similar to those recorded above.

Lactic acid (0·05 mol.) in water (25 ml.) with sodium bismuthate (0·01 mol.) and phosphoric acid (6 ml. of 3½M.) was rapidly oxidised, the mixture becoming warm. The evolved gases were led into a solution of 2 : 4-dinitrophenylhydrazine (0·01 mol.) in sulphuric acid (2 ml.) and alcohol (15 ml.), and when the reaction slackened the remainder of the aldehyde was driven over by warming while passing a stream of nitrogen, yielding acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 148° (1·8 g., 72% calc. on the sodium bismuthate). By use of equivalent amounts of freshly diluted lactic acid and sodium bismuthate, the reaction virtually stopped when about two-thirds of the oxidising agent had been used up, all the free lactic acid presumably having been consumed.

threo-9 : 10-Dihydroxystearic acid, m. p. 95—96° (0·01 mol.), prepared by the method of Scanlan and Swern (*loc. cit.*), in glacial acetic acid (15 ml.) was shaken at 40—45° with sodium bismuthate (0·01 mol.) until the latter was reduced (5½ hours). The product was transferred to a separator with water (40 ml.) and extracted with benzene (100-, 20-, and 20-ml. portions). To the water-washed extract was added a solution of 2 : 4-dinitrophenylhydrazine in the minimum of warm (purified) dioxan, and the mixture

was refluxed for 10 minutes and cooled. After some hours, excess of reagent (*ca.* 1 g.) was filtered off and the solution was distilled to dryness on the water-bath. The residue, dissolved in warm methyl alcohol (25 ml.), was warmed gently with potassium hydrogen carbonate (2 g.) in water (10 ml.), and water (150 ml.) was added. The precipitate (2·0 g., 62%) was recrystallised from methyl alcohol or technical 2-ethoxyethanol to give pelargonaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 106°, as yellow needles. Acidification of the alkaline filtrate with hydrochloric acid, and recrystallisation from alcohol gave *azelaic aldehyde-acid* 2 : *4-dinitrophenylhydrazone* (1·7 g., 48%) as golden-yellow crystals, m. p. 122—122·5° (Found : C, 51·8; H, 5·7; N, 15·3. $C_{15}H_{18}O_6N_4$ requires C, 51·1; H, 5·7; N, 15·9%).

Benzoin (0·01 mol.), sodium bismuthate (0·01 mol), glacial acetic acid (12 ml.), and phosphoric acid (6 ml. of 3½M.) were shaken at 40—50°, reaction requiring 2 hours. After filtration, the mixture was steam-distilled. The distillate (250 ml.) yielded benzaldehyde phenylhydrazone (79%). The residue from the distillation yielded benzoic acid (0·25 g., 22%) and unchanged benzoin (0·1 g.). Analogous experiments, in which phosphoric acid was omitted or dioxan–aqueous phosphoric acid was used, gave similar results, as did working up by solvent extraction. 4-Methoxybenzoin similarly gave benzaldehyde phenylhydrazone, m. p. 157° (1·25 g., 64%), *p*-anisic acid, m. p. 184° (0·85 g., 56%), and unchanged 4-methoxybenzoin (0·6 g.).

Glycerol (0·03 mol.) in water (25 ml.) with phosphoric acid (6 ml. of 3½M.) reduced sodium bismuthate (0·01 mol.) within 2 or 3 minutes at room temperature. The bismuth phosphate was filtered off and washed with water. Half of the filtrate (25 ml.) was heated on the water-bath for 10 minutes with dimedon (0·005 mol., 2·8 g.) in alcohol (10 ml.) and then cooled, and the crystals (*A*) filtered off; the filtrate similarly treated with a further 0·005 mol. of dimedon gave a further crop of crystals (*B*). (*A*), m. p. *ca.* 180°, consisted mainly of the formaldehyde derivative; (*B*), m. p. 200—215°, mainly of the glycollaldehyde derivative. Heating (*A*) with 65% alcohol (15 ml.) and filtering hot left the formaldehyde compound, m. p. 189—190° (2·1 g.), and similar treatment of (*B*) with 70% alcohol (20 ml.) left a residue of 0·4 g. of the same (total yield 86%). The alcoholic extracts on cooling deposited respectively 0·5 and 1·4 g. of fairly pure glycollaldehyde derivative, m. p. 215—220°, and a further small amount was obtained from the mother-liquors; this crude material on digestion with hot benzene (5 ml.) gave a pure *anhydride* (1·75 g., 54%), glistening scales (from 70% alcohol), m. p. 228—229° (Found : C, 71·5; H, 8·0. $C_{12}H_{16}O_4$ requires C, 71·9; H, 7·95%), derived from 2 : 2-di-(2 : 6-diketo-4 : 4-dimethylcyclohexyl)ethanol. Since the formaldehyde–dimedon compound is readily soluble, and the glycollaldehyde derivative is only sparingly soluble in warm benzene, and the reverse is the case with warm 70% alcohol, the two-stage formation of the derivatives was probably unnecessary.

Benzyloxyacetaldehyde.—Carefully fractionated glycerol 1-benzyl ether (b. p. 157·5°/3 mm.; Fairbourne, Gibson, and Stephens, *J.*, 1931, 456, give b. p. 164—166°/2 mm.) (60·7 g., ½ mol.) was stirred with water (250 ml.) and sodium bismuthate (½ mol.) while a solution of phosphoric acid (110 g. of 85%) in water (20 ml.) was added gradually during ½ hour, the temperature being kept at 17—18° by a good cooling-bath. The bath was then removed and stirring continued until the suspension was white, requiring a further ½ hour, during which the temperature rose to 21°. The mixture was extracted with ether (500 ml.) without removal of the bismuth phosphate. The ethereal solution was washed with, successively, water, potassium hydrogen carbonate solution, and water, and evaporated. Water was removed by distillation with benzene, and the residue was fractionally distilled through a 14-cm. Fenske column, yielding benzyloxyacetaldehyde, b. p. 121°/15 mm., 112°/10 mm. (34 g., 68%) (Palfray and Sabetay, *Bull. Soc. chim.*, 1937, **4**, 950, give b. p. 115°/15 mm.) [Found : equiv. (hydroxylamine hydrochloride titration), 151·4. Calc. for $C_9H_{10}O_2$: equiv., 150], and materials, b. p. 112°/10 mm. to 170°/5 mm. (1·7 g.), and 170°/5 mm., presumably unchanged glycerol benzyl ether (7·5 g.). The aldehyde gave an oxime, tablets, m. p. 64—65°.

Ethyl Glyoxylate Alcoholate.—Redistilled ethyl tartrate, b. p. 156·5°/12 mm. (51·5 g., 0·25 mol.), was stirred with water (120 ml.) and sodium bismuthate (0·25 mol.), and a solution of phosphoric acid (80 g. of 85%) in water (20 ml.) was added gradually during ½ hour, the temperature being kept at 35—40°, and then the reaction was completed by stirring for a further ½ hour at 35°. The bismuth phosphate was filtered off and washed with alcohol, the filtrate treated with calcium carbonate (30 g.) and again filtered, the cake being washed with alcohol. The filtrate (540 g.) was concentrated by distillation, finally at *ca.* 30°/20—30 mm., through a Vigreux column. After addition of alcohol (100 ml.) and excess of benzene the solution was decanted from salts. Water and alcohol were removed azeotropically through a 28-cm. Fenske column, and the product was distilled under reduced pressure. The fraction of b. p. *ca.* 79°/30 mm. was redistilled at atmospheric pressure through a small Fenske column, giving ethyl glyoxylate alcoholate, b. p. 137·5° (lit., 136—138°) (37·5 g., 51%). Fractionation was very sharp when excess of benzene was used in the azeotropic distillation, but much less so if excess of alcohol was present.

Adipic Dialdehyde and its Cyclic Monoacetal with cis-cyclo*Hexanediol.*—A solution of *trans-cyclo*hexane-1 : 2-diol, m. p. 103° (29 g., 0·25 mol.) in a mixture of water (75 ml.) and phosphoric acid (100 ml. of 3½M.) was covered with sodium-dried ether (125 ml.), and sodium bismuthate (0·125 mol.) was added in 2 portions with stirring, the temperature being kept at 30°. When reduction was almost complete, a further 50 ml. of 3½M-phosphoric acid was added and then the remaining sodium bismuthate (0·125 mol.) in 2 portions, and stirring was continued at 30° until the reaction was ended (*ca.* 1 hour). Without filtration, the mixture was transferred to a separator with water, the ethereal layer separated, and the aqueous phase extracted with ether (2 × 100 ml.). The ethereal extract was washed with a little water, dried (Na_2SO_4), and evaporated, and the product distilled under reduced pressure through a 14-cm. Fenske column, giving adipic dialdehyde, b. p. 97·5°/12 mm. (14 g., 49%) (oxime m. p. 177—178°), and a resinous residue. The mobile aldehyde became viscous on storage.

In a similar experiment with the *cis*-diol, m. p. 97·5—99° (29 g.), the bismuthate was not completely reduced even after 2 hours and the action seemed to have stopped. On working up, the products (yield 55%) consisted of adipic dialdehyde, b. p. 97·5°/12 mm. (23%), and cis-1 : 2-(*5-formyl*-1 : 2-*pentylidenedioxy*)cyclo*hexane*, b. p. 130°/1 mm. (33%), there was practically no resinous residue from the distillation, and the adipic dialdehyde did not become viscous on storage for some weeks. The

cyclic acetal was a colourless, mobile liquid, lacking the characteristic odour of adipic aldehyde (Found: C, 67·6; H, 9·4. $C_{11}H_{20}O_3$ requires C, 67·8; H, 9·5%). Addition of the acetal-aldehyde (0·006 mol.) to a solution of 2 : 4-dinitrophenylhydrazine (0·005 mol.) in purified dioxan (10 ml.), concentration, and addition of a little cineole to induce crystallisation gave the corresponding 2 : 4-*dinitrophenylhydrazone*, as small bright orange crystals, m. p. 100—101·5°; a small amount of impurity was readily removed by running the solution in benzene containing 1·5% of ethyl alcohol through an alumina column, the hydrazone travelling as a dark brown band. The pure material crystallised as golden plates, m. p. 102—103° (Found: C, 54·7; H, 6·2; N, 14·0. $C_{17}H_{24}O_6N_4$ requires C, 55·1; H, 6·2; N, 14·3%). Warming the acetal-aldehyde in aqueous alcohol with hydroxylamine hydrochloride and neutralisation with sodium hydroxide gave adipic dialdehyde dioxime (white crystals from technical 2-ethoxyethanol), m. p. 177—178° (Found: C, 50·2; H, 8·4; N, 17·7. Calc. for $C_6H_{12}O_2N_2$: C, 50·0; H, 8·4; N, 19·4%).

Pelargonaldehyde and Azelaic Aldehyde-acid.—To *threo*-9 : 10-dihydroxystearic acid, m. p. 95—96° (31 g., 0·1 mol.), in acetic acid (150—200 ml.) sodium bismuthate (0·105 mol.) was added in (four) half-hourly portions, with stirring at 55°, and the mixture was stirred at this temperature until a clear solution resulted (2½ hours) (reaction time *ca.* 5½ hours at 45°, 2 hours at 55—60°). After dilution with water (200 ml.) the reaction products were extracted with benzene (30, 25, and 20 ml.), the benzene solution depositing *ca.* 1 g. of unchanged acid when kept at 0°; ether-extraction, as used by Scanlan and Swern (*loc. cit.*) at an analogous stage, is much less suitable owing to the unfavourable partition coefficient of acetic acid between ether and water. The benzene solution was steam-distilled, about 400 ml. of distillate being collected. The separated benzene layer yielded on evaporation and distillation, pelargonaldehyde, b. p. 95°/23 mm. (7·5 g., 53%), which gave a 2 : 4-dinitrophenylhydrazone, m. p. 106°, and an oxime, m. p. 62—63°. Evaporation of a benzene extract of the residue from the steam-distillation yielded a yellow oil (16·5 g.), crude azelaic aldehyde-acid, which formed a crystal magma on storage. Vacuum-distillation of this material yielded only 3 g. of azelaic aldehyde-acid (b. p. *ca.* 145°/3 mm., m. p. *ca.* 35°), which gave a 2 : 4-dinitrophenylhydrazone, m. p. 122—122·5°. The residue contained considerable amounts of azelaic acid. Alternatively, the initial benzene extract was directly vacuum-distilled through a 14-cm. Fenske column, yielding successively pelargonaldehyde (44%), pelargonic acid (8%), and azelaic aldehyde-acid (15%). While pelargonaldehyde isolated by the steam-distillation procedure remained unchanged on storage, that obtained by direct fractionation of the oxidation products soon set to a mass of needles of the trimer, m. p. 34° (lit., m. p. 28°), which readily recrystallised from alcohol (Found: C, 75·9; H, 12·6. Calc. for $C_{27}H_{54}O_3$: C, 76·0; H, 12·8%).

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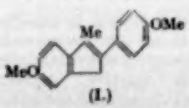
390. *Experiments Relating to Œstrogenic Indenes.*

By D. S. MORRIS.

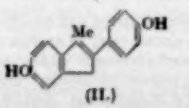
A new synthesis of β-*m*-methoxyphenyl-α-*p*-methoxyphenylpropionic acid is described. Some new indenes have been prepared and shown to possess slight œstrogenic activity.

β-*m*-METHOXYPHENYL-α-*p*-METHOXYPHENYLPROPIONIC acid has previously been prepared by Solmmsen (*J. Amer. Chem. Soc.*, **1943, 65**, 2370) and by Silverman and Bogert (*J. Org. Chem.*, **1946, 11**, 34; cf. Davies and Morris, *J.*, **1947**, 1697) as an intermediate in the synthesis of œstrogenic indenes. It is now shown that *m*-nitro-α-*p*-nitrophenylcinnamic acid is readily prepared by the Perkin reaction and reduced to the diamino-acid catalytically or by ammoniacal hydrogen sulphide. When diazotised, etc., this is converted into the hydroxy-acid, which on further reduction and methylation yields β-*m*-methoxyphenyl-α-*p*-methoxyphenylpropionic acid.

Silverman and Bogert, and Solmmsen (*loc. cit.*) experienced difficulty in the demethylation of (I) to (II). They observed that (II) was unstable in the free state (probably giving a quinone)



(I.)



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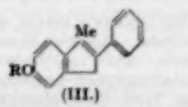


(III.)

but that its diacetate was stable. After failure by many other methods Silverman and Bogert obtained (II), but only in 2—3% yield, by essentially the same technique as that use by Solmmsen, *i.e.*, by heating the dimethoxy-compound with hydrobromic acid in an atmosphere of carbon dioxide. Solmmsen's preparation was, however, shown by Silverman and Bogert to be impure. It was considered that dealkylation might be achieved in better yields if the process could be accomplished with simultaneous acetylation since the diacetate of (II) is reported to be stable, and that dealkylation of such indenes possessing alkoxy-groups other than methoxy might be

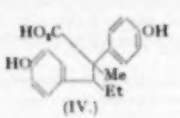
carried out more readily (cf. Trownow and Ladinga, *Ber.*, 1929, **62**, 2844). However, neither hydrogen iodide in presence of acetyl iodide nor hydrogen bromide in presence of acetic anhydride successfully dealkylates the analogous indenes (III) and it would appear that the presence of water is necessary for this operation. Nevertheless it has been demonstrated that the 6-*iso*propoxyindene is more readily dealkylated than the 6-methoxyindene and it is reasonable to suggest that the use of the *iso*proxy-ethers may result in better yields of dihydroxy-indenes.

Dealkylation of 6-*iso*propoxy-2-phenyl-3-*p*-methoxyphenylindene gave an incompletely demethylated substance, probably 6-hydroxy-2-phenyl-3-*p*-hydroxyphenylindene contaminated with the corresponding 3-*p*-methoxy-analogue.

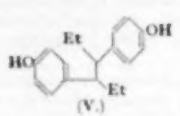
By the use of appropriate reactants with sodium phenylacetate in acetic anhydride, *m*-methoxy-, *m*-*iso*propoxy-, *m*-benzyloxy-, and *m*-hydroxy-α-phenylcinnamic acid were prepared. These cinnamic acids, except the *m*-benzyloxy-acid, were hydrogenated to the corresponding propionic acids when the sodium salts were used in aqueous solution with Raney nickel as catalyst; the free acids resisted hydrogenation in alcohol. Hydrogenolysis of *m*-benzyloxy-α-phenylcinnamic acid accompanied hydrogenation of the double bend and the product isolated was 1-phenyl-2-*m*-hydroxyphenylpropionic acid. 1-Phenyl-2-*m*-methoxy- and -2-*m*-*iso*propoxy-phenylpropionic acid were readily cyclised to 5-methoxy-* and 5-*iso*propoxy-2-phenyl-indanone respectively, and these in turn were converted into 6-methoxy- and 6-*iso*propoxy-2-phenyl-3-methylindene. 1-Phenyl-2-*m*-benzyloxyphenylpropionic acid was prepared by benzylation of the hydroxy-acid, but attempts at cyclisation by stannic chloride resulted in debenzylation; a trace of a ketonic phenolic substance was found in the alkali-soluble fraction, but the 2 : 4-dinitrophenylhydrazone isolated was impure. Phosphoric oxide and a solution of the acid in benzene was likewise unsatisfactory and ice-cold concentrated sulphuric acid caused debenzylation. Two alternative approaches were made to 5-benzyloxy-2-phenylindanone. The first consisted of an attempt to protect the phenolic group of 1-phenyl-2-*m*-hydroxyphenyl-propionic acid by benzoylation; however, the phenolic group in this acid was highly unreactive towards benzoyl chloride in pyridine and the sole acidic reaction product was benzoic acid. The second consisted of the acetylation of α-phenyl-*m*-hydroxy- to α-phenyl-*m*-acetoxy-cinnamic acid which was hydrogenated in acetic acid in presence of platinum oxide catalyst, presumably to the corresponding propionic acid. The last, an oil, was treated with stannic chloride but failed to yield a ketonic product.

It is worth noting that many of the cyclisations carried out in this field might have been more effectually performed if liquid hydrogen fluoride had been available (Johnson, "Organic Reactions," Vol. II, p. 157; Solmmsen and Wenis, *J. Amer. Chem. Soc.*, 1948, **70**, 4197).

Substituted α-phenylcinnamic acids have not previously been examined for activity, despite their stilbenoid structure. Hunter and Kormann (*J. Amer. Chem. Soc.*, 1948, **70**, 3424) have recently reported that αβ-di-(*p*-hydroxyphenyl)-α-methylvaleric acid (IV) is active; it combines structural characteristics common to hexœstrol (V) and doisynolic acid (VI), and may also be regarded as a substituted β-phenylpropionic acid.



(IV.)



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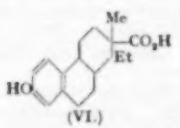

(VI.)

The biological assays, which were carried out by Dr. J. M. Robson, will be reported in detail elsewhere. However it may be stated that in initial assays (5 mg. per mouse) *m*-hydroxy-α-phenyl- and -α-*p*-hydroxyphenyl-cinnamic acid, and α-phenyl-β-*m*-hydroxyphenyl- and α-*p*-methoxyphenyl-β-*m*-methoxyphenyl-propionic acid were inactive. Activity at the 5-mg. level were observed with 6-methoxy- and 6-hydroxy-2-phenyl-3-methylindene and with 6-hydroxy-2-phenyl-3-*p*-hydroxyphenylindene. 6-*iso*Propoxy-2-phenyl-3-*p*-methoxy-phenylindene exhibited no activity. None was active at the 1-mg. level.

Experimental.

m-Nitro-α-p-nitrophenylcinnamic Acid.—Potassium *p*-nitrophenylacetate was prepared by addition of an alcoholic solution of *p*-nitrophenylacetic acid (18·1 g.) to an aqueous solution of potassium carbonate (6·9 g.), followed by evaporation to dryness under reduced pressure. The residue of crude potassium

* For assignment of structure see Silverman and Bogert (*loc. cit.*).

salt thus obtained was refluxed for 8 hours with acetic anhydride (260 c.c.), *m*-nitrobenzaldehyde (15·1 g.), and pyridine (1 c.c.), in an oil-bath at 150—160°. The product was cooled somewhat, diluted with water, digested on the water-bath for 30 minutes, and cooled to room temperature. The residue obtained by filtration was extracted with hot aqueous sodium carbonate, and the mixture filtered and acidified with dilute hydrochloric acid to yield a crude acidic product which was filtered off and washed with a little cold alcohol. When crystallised from methyl alcohol the crude *acid* gave pale yellow prisms (19 g.), m. p. 222° (Found: C, 57·3; H, 3·3; N, 8·5. $C_{15}H_{10}O_5N_2$ requires C, 57·3; H, 3·2; N, 8·9%).

m-Amino-α-p-aminophenylcinnamic Acid.—(a) *By hydrogenation of the dinitro-acid.* The above acid (18·4 g.) in methyl alcohol (500 c.c.) was hydrogenated at room temperature and pressure in presence of Raney nickel (20 g.). Six moles of hydrogen were absorbed. Removal of the catalyst and most of the solvent gave the *amino-acid* as glistening brown plates (10 g.), m. p. 208° (from methyl alcohol). When exposed to air the plates changed to a yellow powder (Found: C, 70·0; H, 5·6; N, 11·9. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%). The *diacetyl* derivative was prepared as pale buff-coloured needles, m. p. 277° (decomp.) (Found: C, 67·0; H, 5·8; N, 7·5. $C_{19}H_{18}O_4N_2$ requires C, 67·5; H, 5·3; N, 8·3%).

(b) *By reduction of the dinitro-acid with ammoniacal hydrogen sulphide.* A stream of hydrogen sulphide was passed through a suspension of the dinitro-acid (1 g.) in aqueous ammonia (20 c.c.; 6*N*.) for 1 hour. The mixture was boiled until the hydrogen sulphide and ammonia were completely expelled, cooled, and filtered, and the solid washed with boiling water. The filtrate when acidified with glacial acetic acid gave an acid (0·3 g.), m. p. and mixed m. p. 207—208°, identical with that obtained by hydrogenation as above.

m-*Hydroxy-α-p-hydroxyphenylcinnamic Acid.*—The crude amine (2·56 g.) in a suspension of dilute sulphuric acid [concentrated acid (3 c.c.) and water (24 c.c.)] was diazotised at 0° with a solution of sodium nitrite (1·4 g.) in water (5 c.c.). The ice-cold solution was added drop-wise to a boiling solution of sulphuric acid [concentrated acid (3 c.c.) in water (24 c.c.)]. The solution was boiled for 10 minutes with a little charcoal and filtered hot. The filtrate when cooled deposited yellowish-brown needles which were recrystallised from hot water to give an *acid* (1·5 g.), m. p. 230° (decomp.) (Found: C, 67·1; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·4; H, 4·7%). Two crystallisations from aqueous alcohol gave pale brown needles of a *hydrate*, m. p. 256° (Found: C, 65·6; H, 4·9. $C_{15}H_{12}O_4,H_2O$ requires C, 65·7; H, 5·1%). The acid (0·5 g.) was shaken with sodium hydroxide (0·25 g.) in water (5 c.c.) and benzoyl chloride (0·7 g.) for 2 hours. The oil obtained was acidified, washed with water, and taken up in ether and the crude acid extracted with sodium carbonate solution. Addition of dilute hydrochloric acid then precipitated the *dibenzoate* which crystallised from aqueous alcohol in small plates, m. p. 195° (Found: C, 75·1; H, 5·0. $C_{29}H_{22}O_6$ requires C, 75·0; H, 4·8%).

Hydrogenation of m-*Hydroxy-α-p-hydroxyphenylcinnamic Acid and Methylation of the Product.*—The acid (0·5 g.) in an excess of aqueous sodium hydroxide was hydrogenated in presence of Raney nickel. The catalyst was removed by filtration, the filtrate acidified with hydrochloric acid and extracted with ether, and the ethereal solution extracted with aqueous sodium hydrogen carbonate. By acidification of the alkaline solution and extraction with ether, an oily acid was obtained which did not readily crystallise. It was soluble in hot water and aqueous alcohol and tended to crystallise from ethyl alcohol. However, when methylated in alkaline solution with an excess of methyl sulphate, a crystalline acid (0·3 g.), m. p. 104°, was obtained. A mixed m. p. with *m*-methoxy-α-*p*-methoxyphenyl-β-*m*-methoxyphenylpropionic acid obtained by an alternative procedure showed no depression.

m-iso*Propoxybenzaldehyde.*—To *m*-hydroxybenzaldehyde (61 g.) in a solution of sodium (11·5 g.) in alcohol (200 c.c.), *iso*propyl bromide (61·5 g.) was added and the mixture refluxed for 5 hours. The residue obtained by removal of the solvent was taken up in ether, washed with dilute sodium hydroxide solution, dried, and distilled, to give an oil (43 g.), b. p. 110—113°/2 mm. (Found: C, 73·6; H, 7·45. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%).

m-*Methoxy-α-phenylcinnamic Acid.*—(a) Sodium phenylacetate (102 g.), *m*-methoxybenzaldehyde (88 g.), and glacial acetic acid (500 c.c.) were heated under reflux at 160° for 6 hours [cf. Solmmsen's procedure (*loc. cit.*) for the analogous preparation using sodium *p*-methoxyphenylacetate]. The product was worked up by pouring it into water and the oil was isolated. The aqueous portion was acidified and gave phenylacetic acid. The oily layer was digested with sodium carbonate solution and extracted with ether. Acidification of the aqueous alkaline portion gave phenylacetic acid as the sole acidic product, and from the ethereal solution *m*-methoxybenzaldehyde was obtained by drying, evaporation, and distillation.

(b) Sodium phenylacetate (15·8 g.), *m*-methoxybenzaldehyde (13·6 g.), anhydrous sodium carbonate (5 g.), pyridine (0·5 c.c.), and acetic anhydride (10·6 c.c.) were heated for 2 hours at 180°. The cooled product was diluted with water (300 c.c.), made alkaline with sodium hydroxide (30 c.c.; 6*N*.), and digested on the water-bath for 30 minutes (cf. the procedure given in "Organic Reactions," Vol. II, p. 262, for the preparation of α-phenylcinnamic acid). The mixture was cooled and extracted with ether and the alkaline layer acidified with dilute hydrochloric acid. The acid product obtained was washed with alcohol and dissolved in sodium carbonate, and the sodium carbonate solution acidified with dilute hydrochloric acid to give a white crystalline product (5 g.), m. p. 191—192° (from ethyl alcohol) (Found: C, 75·0; H, 5·8. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

(c) *m*-Methoxybenzaldehyde (30 g.), sodium phenylacetate (25·2 g.), acetic anhydride (34 g.), and pyridine (1 c.c.) were refluxed for 8 hours at 160—170°. On working up of the product as in (*b*) above, the acid (20 g.), m. p. 191—192°, was obtained [this method involved using an excess of the aldehyde and was based on the procedure of Bacharach and Brogan (*J. Amer. Chem. Soc.*, 1928, **50**, 3533) for the preparation of cinnamic acid].

m-iso*Propoxy-α-phenylcinnamic Acid.*—*iso*Propoxybenzaldehyde (41 g.), sodium phenylacetate (40 g.), acetic anhydride (150 c.c.), and pyridine (1 c.c.) were heated under reflux for 5 hours at 150—160°. The product was cooled somewhat, diluted with water (200 c.c.), boiled for 10 minutes, diluted with more water (200 c.c.) and thoroughly cooled. A white crystalline mass was formed which was soluble in hot, but insoluble in cold, alkali; acidification of its aqueous solution gave a crude *acid* which was washed with cold alcohol (100 c.c.) and finally crystallised from hot alcohol (400 c.c.) to give pale yellow needles (38 g.), m. p. 159° (Found: C, 76·5; H, 5·9. $C_{19}H_{18}O_3$ requires C, 76·6; H, 6·4%).

m-Benzyloxy-α-phenylcinnamic Acid.—*m*-Benzyloxybenzaldehyde (Rapson and Robinson, *J.*, 1935, 1533) (21·2 g.), sodium phenylacetate (15·8 g.), acetic anhydride (200 c.c.), and pyridine (1 c.c.), heated at 150—160° for 5 hours, gave an *acid* (19 g.), m. p. 181—182° (Found: C, 80·2; H, 5·5. $C_{23}H_{18}O_3$ requires C, 80·6; H, 5·3%).

m-Hydroxy-α-phenylcinnamic Acid.—*m*-Hydroxybenzaldehyde (24·4 g.), sodium phenylacetate (31·6 g.), acetic anhydride (130 c.c.), and pyridine (0·5 c.c.) were refluxed for 8 hours at 150—160°. The mixture was cooled somewhat, diluted with water (200 c.c.), and digested on the water-bath for 10 minutes. When thoroughly cooled, a solid product was filtered off and digested with sodium hydroxide solution for 30 minutes. A crude *acid* was obtained by acidification, dissolved in sodium carbonate solution, treated with charcoal, and acidified to give needles (28 g.), m. p. 187—188° (Found: C, 74·5; H, 5·3. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

α-Phenyl-β-m-methoxyphenylpropionic Acid.—A solution of *m*-methoxy-α-phenylcinnamic acid (19 g.) in dilute sodium carbonate solution was made just alkaline to phenolphthalein. When this was shaken with hydrogen at room temperature and pressure in presence of Raney nickel (5 g.), the theoretical amount of hydrogen was absorbed. Removal of the catalyst and acidification gave an oil (19 g.), a portion of which was purified for analysis by high-vacuum distillation, having b. p. 190—200°/0·4—0·6 mm. (Found: C, 74·8; H, 6·4. $C_{16}H_{14}O_3$ requires C, 75·0; H, 6·25%).

α-Phenyl-β-m-isopropoxyphenylpropionic Acid.—*m-iso*Propoxy-α-phenylcinnamic acid was hydrogenated as in the previous hydrogenation and gave prisms, m. p. 86°, from alcohol (Found: C, 76·0; H, 7·2. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1%).

α-Phenyl-β-m-benzyloxyphenylpropionic Acid.—α-Phenyl-β-*m*-benzyloxyphenylcinnamic acid, hydrogenated as above, absorbed two moles of hydrogen and the product contained benzyl alcohol and an acidic oil, b. p. 150—153°/0·1 mm. (Found: C, 74·4; H, 5·9. $C_{16}H_{14}O_3$ requires C, 74·4; H, 5·8%). After a long time, the oil solidified to needles m. p. 75°, identical with *α-phenyl-β-m-hydroxyphenylpropionic acid* obtained by hydrogenation, in a like manner, of *m*-hydroxy-α-phenylcinnamic acid. The propionic acid (20 g.) in alcohol (50 c.c.) was added to a solution of sodium (3·8 g.) in absolute alcohol (50 c.c.). Benzyl bromide (27·2 g.) was added and the mixture refluxed for 5 hours. The mixture was diluted with water, made alkaline with sodium hydroxide solution (40 c.c.; 10%), and digested on the water-bath for 2 hours. The product was taken up in ether, and the alkaline layer was separated and acidified to give an oil which was crystallised from methyl alcohol to give needles (12 g.), m. p. 111—112° (Found: C, 79·1; H, 5·6. $C_{23}H_{20}O_3$ requires C, 79·5; H, 6·0%).

5-Methoxy-2-phenylindanone.—α-Phenyl-β-*m*-methoxyphenylpropionic acid (19 g.) in dry ether (100 c.c.) containing pyridine (3 drops), and thionyl chloride (10 g.) were warmed on the water-bath for 30 minutes. The solution was evaporated to dryness under reduced pressure, thrice treated with dry benzene (50 c.c.), and evaporated to dryness after each addition. The residue was dissolved in dry benzene (100 c.c.), and the solution cooled to 5° and treated with a solution of stannic chloride (22 g.) in benzene (25 c.c.). After 90 minutes with intermittent shaking, the product was worked up by pouring it on ice and extraction in ether. The ethereal solution was washed successively with dilute hydrochloric acid, water, and sodium carbonate solution, dried (Na_2CO_3), and evaporated, to give an oil which crystallised from alcohol in small needles (12 g.), m. p. 115° (Found: C, 80·1; H, 5·9. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* formed orange-red needles, m. p. 236°, from alcohol (Found: C, 63·1; H, 4·2; N, 14·4. $C_{22}H_{18}O_5N_4$ requires C, 63·0; H, 4·3; N, 13·4%).

*5-iso*Propoxy-2-*phenylindanone.*—Reaction as in the preceding paragraph gave this *ketone* as prisms (14 g.), m. p. 124—125° (Found: C, 81·0; H, 7·2. $C_{18}H_{18}O_2$ requires C, 81·3; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* formed orange-red plates, m. p. 227—228°, from aqueous alcohol (Found: N, 12·0. $C_{24}H_{22}O_5N_4$ requires N, 12·6%).

6-*Methoxy*-2-*phenyl*-3-*methylindone.*—5-Methoxy-2-phenylindanone (8 g.) in toluene (100 c.c.) was added to methylmagnesium iodide prepared from methyl iodide (9·6 g.), magnesium (1·6 g.), and ether (50 c.c.). The same procedure was used as in the previously described Grignard reactions and the *indene* was obtained as needles (8 g.), m. p. 98—99° (from alcohol) (Found: C, 86·7; H, 6·9. $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%).

6-*iso*Propoxy-2-*phenyl*-3-*methylindone.*—5-*iso*Propoxy-2-phenylindanone (2 g.) similarly gave this *indene* as plates (2 g.), m. p. 86° (from alcohol) (Found: C, 85·6; H, 7·2. $C_{19}H_{20}O$ requires C, 86·4; H, 7·6%).

6-*iso*Propoxy-2-*phenyl*-3-p-*methoxyphenylindene.*—Prepared similarly, this *indene* was obtained as needles (1·4 g.), m. p. 145—146° (from alcohol) (Found: C, 83·7; H, 6·9. $C_{25}H_{24}O_2$ requires C, 84·3; H, 6·7%).

Attempted Cyclisation of α-Phenyl-β-m-benzyloxyphenylpropionic Acid.—(*a*) By the technique used in the previous cyclisations, α-phenyl-β-*m*-benzyloxyphenylpropionic acid (4·5 g.) was converted into the acid chloride [by thionyl chloride (2 g.)] and treated in cold benzene with stannic chloride (5 g.). When worked up as before, the non-acidic fraction (4 g.) consisted of a gum containing benzyl chloride and no ketonic derivatives could be prepared. The alkali-soluble fraction (0·2 g.) was divided into two portions, one which was soluble in aqueous sodium carbonate and the other in aqueous sodium hydroxide. The former on long storage in aqueous-alcoholic solution afforded α-phenyl-β-*m*-hydroxyphenylpropionic acid, m. p. and mixed m. p. 75°. The latter gave rise to an unidentified 2 : 4-dinitrophenylhydrazone, m. p. 192° (darkens at 140°) (crystallised from aqueous alcohol) (Found: C, 58·2; H, 4·4; N, 14·2. $C_{21}H_{16}O_5N_4$ requires C, 62·4; H, 4·0; N, 13·9%).

(*b*) α-Phenyl-β-*m*-benzyloxyphenylpropionic acid (1 g.), phosphoric oxide (2 g.), and benzene (50 c.c.), heated on the water-bath for 1 hour, gave a non-acidic gum from which no ketonic derivative could be prepared.

(*c*) The acid (1 g.) was slowly added to concentrated sulphuric acid (2 c.c.) at −5° and stirred for 30 minutes, the temperature being kept below 0°. The mixture was poured on ice and the acid extracted with sodium carbonate solution. None of the starting material was recovered and the oily acid obtained slowly crystallised after 2 weeks. The m. p. and mixed m. p. identified the product as *m*-hydroxy-α-phenylcinnamic acid.

Attempts to Dealkylate 6-Alkoxyindenes.—(*a*) 6-Methoxy-2-phenyl-3-methylindene (1 g.), glacial acetic acid (15 c.c.), and acetyl iodide (3 c.c.) containing 12% of hydrogen iodide, heated under reflux for 5 minutes, afforded only gums and none of the original indene was recovered. A similar result was observed when the 6-*iso*propoxyindene was used and when either indene was treated in a similar manner on the water-bath.

(*b*) The 6-methoxyindene (0·5 g.), glacial acetic acid (10 c.c.), acetic anhydride (1 c.c.), and 30% hydrogen bromide in acetic acid (2 c.c.) were refluxed for 10 minutes. The mixture was cooled and poured on ice. A crystalline product was obtained which was washed with water and boiled with aqueous alkali for 30 minutes. The alkali-soluble fraction crystallised as pale greenish-brown needles (5 mg.), m. p. 152—153°. Analysis indicated that this compound was probably the impure 6-indenol (Found: C, 82·7; H, 6·7. Calc. for $C_{18}H_{14}O$: C, 86·5; H, 6·3%). From the neutral fraction the 6-methoxyindene (0·48 g.) was obtained by crystallisation from aqueous alcohol.

(*c*) The 6-*iso*propoxyindene was treated as in (*b*); no phenolic product was isolated though a faint turbidity was observed when the alkaline extract was acidified.

When a longer time of heating was used neither the 6-methoxy- nor the 6-*iso*propoxy-indene was recovered and no phenolic product was obtained.

(*d*) A solution was prepared by mixing hydrogen bromide in acetic acid (15 c.c. of 50%) with acetic acid (70 c.c.) and water (15 c.c.). This solution (20 c.c.) was used in the dealkylation experiments shown in the table below. The indene (1 g.) was heated under reflux in an atmosphere of nitrogen and then separated into phenolic and neutral fractions by dilution with water and extraction with sodium hydroxide.

Indene.	Reflux time, hours.	Phenolic fraction, mg.	Neutral fraction, mg.	M. p. of phenolic fraction.
6-Methoxy-	1	Only turbid (*ca.* 2 mg.)	950	—
6-*iso*Propoxy-	1	20	900	148—149°
6-Methoxy-	4	110	800	148
6-*iso*Propoxy-	4	460	200	147—148

The phenolic fractions were combined and crystallised from aqueous alcohol to give a pale buff-coloured powder, m. p. 154—155° (Found: C, 86·4; H, 6·3. $C_{18}H_{14}O$ requires C, 86·5; H, 6·3%). The respective neutral fractions from these experiments, with the exception of the last, were shown to be the original 6-alkoxyindenes. In the last experiment only, an oil was obtained from the neutral fraction.

Dealkylation of 6-*iso*Propoxy-2-phenyl-3-*p*-methoxyphenylindene.—The indene (0·5 g.) was heated under reflux with the hydrogen bromide solution (3 c.c.) for 4 hours and the product isolated as before. The crude phenolic fraction (0·35 g.) was a buff-coloured solid and was purified by percolation in ether–benzene through a column of alumina. Elution with benzene–alcohol was necessary and the product was finally obtained as a buff-orange powder (0·25 g.), m. p. 225—230°, from aqueous alcohol (Found: C, 83·7; H, 5·5. $C_{31}H_{18}O_3$ requires C, 84·0; H, 5·3%). Dealkylation was incomplete (Found: OMe, 1·3. $C_{31}H_{17}O_3$ requires OMe, 9·8%).

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391. *The Synthetic Application of Phenylarsinebis(magnesium Bromide). Part I. The Synthesis of* iso*Arsindolines, Tetrahydroisoarsinolines, and 2-Arsaperinaphthanes.*

By M. H. Beeby, Gerald H. Cookson, and Frederick G. Mann.

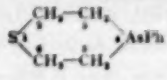
It is shown that the above Grignard reagent, $Ph{\cdot}As(MgBr)_2$, reacts with *o*-xylylene dibromide and dichloride to give 2-phenyliso*arsindoline* and with *o*-(2-bromoethyl)benzyl bromide to give 2-phenyl-1 : 2 : 3 : 4-tetrahydroiso*arsinoline*. The high yield of each compound makes this method of preparation superior to previous methods. The reagent also reacts with 1 : 8-bis-bromomethylnaphthalene to give 2-phenylarsaperinaphthane, which represents a new type of heterocyclic arsenic compound. The probable mechanism of the formation of these compounds is briefly discussed.

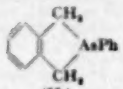
Phenylarsinebis(magnesium bromide), $Ph{\cdot}As(MgBr)_2$, was first prepared by Job and Reich (*Compt. rend.*, 1923, **177**, 56) by the interaction of phenylarsine, $Ph{\cdot}AsH_2$, and ethylmagnesium bromide in ethereal solution. Later, Job, Reich, and Vergnaud (*Bull. Soc. chim.*, 1924, **35**, 1404) showed that this reagent reacted with 2 : 2′-dichlorodiethyl sulphide to form 4-phenylthiarsine (I) in 7% yield. Blicke and Oneto (*J. Amer. Chem. Soc.*, 1935, **57**, 749) have similarly prepared diphenylarsinemagnesium bromide, $Ph_2As{\cdot}MgBr$, using however phenylmagnesium bromide advantageously in place of ethylmagnesium bromide.

Phenylarsinebis(magnesium bromide), prepared by Blicke and Oneto's modified method,

i.e., by the interaction of phenylarsine and phenylmagnesium bromide, has recently been used by Cookson and Mann (*J.*, 1949, 2888) for converting *o*-phenylbenzyl bromide, Ph·C_6H_4·CH_2Br, into phenylbis-*o*-phenylbenzylarsine, Ph·As(CH_2·C_6H_4Ph)$_2$, in almost theoretical yield. We have now investigated its use for the preparation of various heterocyclic derivatives of arsenic on the lines of Job, Reich, and Vergnaud's earlier work.

It has been shown by Lyon and Mann (*J.*, 1945, 30) and by Lyon, Mann, and Cookson (*J.*, 1947, 662) that 2-phenyl*iso*arsindoline (II) can be prepared either by the action of *o*-xylylene dibromide, $C_6H_4(CH_2Br)_2$, on phenyldichloroarsine in the presence of sodium, or by the thermal decomposition of the quaternary salt which the dibromide forms with phenyldimethylarsine.


(I.)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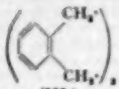
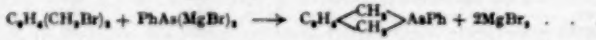

(III.)

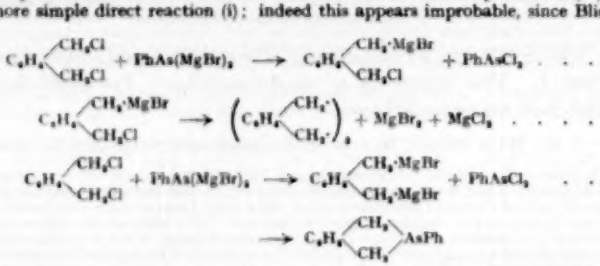
These methods furnish the crude *iso*arsindoline (II) in 19% and 60% yield respectively. We now find that a third synthetic route is available, for *o*-xylylene dibromide reacts with a cold solution of phenylarsinebis(magnesium bromide) to give the crude *iso*arsindoline in 80% yield. This method is therefore the most efficacious of the three.

It would appear from this result that the reaction is of the simple character:


. . . (i)

When however this reaction was carried out with *o*-xylylene dichloride instead of the dibromide, the *iso*arsindoline (II) was obtained in 40% yield, the other products isolated being phenyldichloroarsine (*ca.* 15%) and also a small quantity of *s*-tribenz*cyclo*dodecatriene (III), the hydrocarbon that Baker, Banks, Lyon, and Mann (*J.*, 1945, 27) had obtained by the action of sodium on *o*-xylylene dibromide.

The origin of the phenyldichloroarsine is uncertain, but the following mechanism for the formation of these by-products is suggested. In addition to the main reaction (i), it is possible that one (or both) of the chlorine atoms of the *o*-xylylene dichloride directly displaces the magnesium bromide portion of the Grignard reagent, with the formation of phenyldichloroarsine (reaction ii). A portion of the *o*-xylylene magnesium derivative undergoes direct decomposition to give the hydrocarbon (reaction iii). If both the chlorine atoms in the *o*-xylylene dichloride undergo replacement by magnesium bromide (reaction iv), the two products may undergo further interaction to form the *iso*arsindoline. It should be emphasised however that there is at present no evidence that the *iso*arsindoline is formed by reaction (iv) rather than by the more simple direct reaction (i); indeed this appears improbable, since Blicke and


. . . (ii)

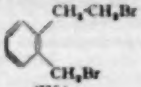
. . . . . (iii)

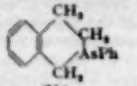
. . (iv)

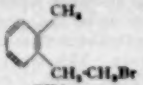
Oneto (*loc. cit.*) state that the di-Grignard reagent, *o*-$C_6H_4(CH_2$·$MgBr)_2$, does not react with diphenylbromoarsine, Ph_2AsBr, whereas *o*-xylylene dibromide reacts readily with diphenylarsinemagnesium bromide, Ph_2As·MgBr, to give the diarsine, *o*-$C_6H_4(CH_2$·$AsPh_2)_2$.

Evidence for the formation of compounds of the type shown in reaction (ii) is provided by the interaction of *o*-(2-bromoethyl)benzyl bromide (IV) and the Grignard reagent. Holliman and Mann (*J.*, 1943, 547) have shown that the dibromide (IV) reacts with phenyldichloroarsine and sodium to give pure 2-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (V) in 31% yield based on the dibromide used. We find furthermore that the dibromide reacts smoothly with cold phenylarsinebis(magnesium bromide) to give the crude *iso*arsinoline (V) in 70% yield. In

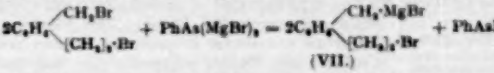
addition to the *iso*arsinoline (V), however, *o*-(2-bromoethyl)toluene (VI) is formed in moderate quantity, and phenyldibromoarsine, $PhAsBr_2$, is also undoubtedly formed although its isolation


(IV.)


(V.)


(VI.)

in the pure state is difficult. It is highly probable that the compound (VI) arises by initial reaction of the bromomethyl group in the dibromide (IV) with the Grignard reagent thus :


(VII.)

This is of course analogous to reaction (ii). The compound (VII), if it underwent no further immediate reaction, would on subsequent hydrolysis give the monobromo-compound (VI). It is clear that the greater reactivity of the bromomethyl group compared with that of the bromoethyl group in the dibromide (IV) would favour the formation of the monomagnesium bromide (VII) : if however a further reaction occurred to a small extent, and both groups were to give this same reaction, the traces of *o*-ethyltoluene which would be formed on hydrolysis would probably escape detection in the subsequent isolation of the products.

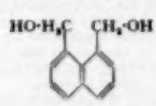
It is noteworthy that, although Job, Reich, and Vergnaud (*loc. cit.*) found that phenylarsinebis(magnesium bromide) reacted with both carbonyl chloride and ethylene dibromide with the formation of arsenobenzene, we find that the above reaction with cold *o*-xylylene dibromide produces no detectable amount of arsenobenzene, and that the cold dibromide (IV)

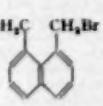
$$PhAsBr_2 + PhAs(MgBr)_2 \longrightarrow PhAs{:}AsPh + 2MgBr_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (v)$$

gives only a very small quantity. When however the dibromide (IV) was added to a benzene solution of the Grignard reagent at 70°, the yield of the crude *iso*arsinoline fell to 38%, and arsenobenzene was formed in 20% yield. It is probable that at this higher temperature the phenyldibromoarsine as fast as it was formed reacted competitively with unchanged phenylarsinebis(magnesium bromide) to form the arsenobenzene (reaction v) : we have some evidence, at present incomplete, that the interaction of these two compounds at room temperature is slow.

Apart from the mechanism of the reactions involved, however, the synthetic value of the Grignard reagent for the production of these cyclic arsines is now manifest. It is noteworthy that when the dibromide (IV) was heated with phenyldimethylarsine, the *iso*arsinoline (V) was formed in only 8% yield, and, for the synthesis of this ring system in particular, the arsine–Grignard method is far superior to the other available methods.

To illustrate further the application of the arsine–Grignard reagent for the synthesis of heterocyclic arsenic systems, we have reduced methyl naphthalate by lithium aluminium


(VII.)


(VIII.)

(IX.)

(X.)

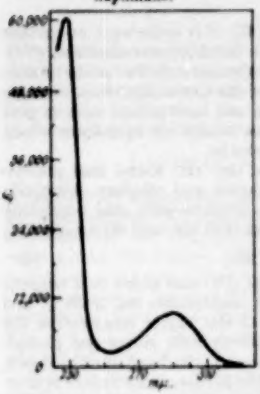
hydride to 1 : 8-bishydroxymethylnaphthalene (VII), and converted this into 1 : 8-bisbromomethylnaphthalene (VIII), a process which, in spite of a wide variation in conditions employed, always gave also the highly stable 2-oxaperinaphthane (alternatively named 1 : 3-naphtho-[1 : 8-*cd*]pyran) (IX). When the dibromo-compound (VIII) was treated under the usual conditions with phenylarsinebis(magnesium bromide), 2-phenylarsaperinaphthane (X; R = Ph) was obtained as an oil which could not be crystallised, nor could it be distilled without decomposition even in a high vacuum. It was characterised as its crystalline methiodide, 2-phenyl-2-methylarsoniaperinaphthane iodide, and as its palladochloride derivative, dichlorodi(2-phenylarsaperinaphthane)palladium, $[(C_{15}H_{15}As)_2PdCl_2]$.

The heterocyclic ring in the 2-phenyl compound (X; R = Ph) possesses considerable stability, because, when this compound is heated with hydriodic acid, the phenyl group is evicted with the formation of 2-iodoarsaperinaphthane (X; R = I). This reaction is precisely

analogous to the conversion of 2-phenylisoarsindoline into 2-iodoisoarsindoline (Lyon, Mann, and Cookson, *loc. cit.*) and of 2-phenylisoarsinoline into 2-iodoisoarsinoline (see later), and it is of considerable synthetic value, as the iodo-group could clearly now be replaced by any desired alkyl or aryl group by the application of the appropriate Grignard reagent.

The absorption spectrum of the methiodide of 2-phenylarsaperinaphthane is shown in the adjoining Figure. This spectrum proved almost completely identical with that of 2-iodoarsaperinaphthane, which in consequence is not depicted. The fact that these spectra should be virtually identical indicates clearly that the absorption is only very slightly affected by the nature of the groups joined to the arsenic, and by the valency state of the arsenic itself. This is further confirmed by the fact that the two marked absorption bands in the spectrum of the methiodide are almost certainly the two typical bands of naphthalene, but displaced to wavelengths longer by 10—12 mμ. This point is of considerable importance, because it provides indirect confirmation for Cookson and Mann's suggestion (*loc. cit.*) that the marked absorption band shown by the methiodide of 10-phenyl-9 : 10-dihydroarsanthridine is probably the characteristic diphenyl band similarly shifted by *ca.* 16 mμ. but (in this case) reduced in intensity. As a corollary, this would provide stronger evidence that the two *o*-phenylene groups in the 9 : 10-dihydroarsanthridine ring system undergo some oscillation about the coplanar position.

Methiodide of 2-phenylarsaperinaphthane.



Considerable further work is required before the complete mechanism of the reaction of phenylarsinebis(magnesium bromide) with organic halides, and also the limitations attending its use, are fully understood. It is noteworthy that we find that, when the arsine–Grignard reagent reacted with either bromoacetonitrile or with bromoacetone diethyl ketal, the only products isolated were arsenobenzene and phenyldibromoarsine. Ethyl bromoacetate gave the same products, but in addition a 5% yield of the required tertiary arsine, phenylbiscarbethoxymethylarsine,

$$PhAs(CH_2{\cdot}CO_2Et)_2;$$

however, since this compound was a liquid it was identified solely as its crystalline palladobromide derivative, dibromodi(phenylbiscarbethoxymethylarsine)palladium, $[(C_{14}H_{19}O_4As)_2PdBr_2]$. Ethylene oxide appeared to react with the Grignard reagent, but no definite products could be isolated.

Experimental.

Phenylarsinebis(magnesium Bromide).—In view of the very ready oxidation of phenylarsine it was always weighed first and the amounts of the other reagents then accordingly adjusted. The technique involved, with typical weights of reagents employed, is described now and applies to all subsequent experiments. A stoppered nitrogen-filled dropping-funnel was weighed, and the phenylarsine (11·1 g.), which had been stored under carbon dioxide, was transferred to the funnel which was again weighed. The transference was most conveniently performed by forcing the arsine by nitrogen pressure up into a vertical nitrogen-filled pipette, the tip of which was then inserted deeply into the funnel before the arsine was released. Under these conditions very little oxidation occurred. For large-scale work, however, the arsine was syphoned directly from the storage vessel to the funnel by nitrogen pressure. Dry benzene (70 c.c.) was then added. Meanwhile a Grignard reagent was prepared by the action of bromobenzene (24·8 g., 2·2 mols.) in ether (45 c.c.) on magnesium (4 g., 2·3 atoms) under ether (7 c.c.). The Grignard reagent was boiled under reflux for 15 minutes and then cooled, and the air displaced by nitrogen. The reagent was then chilled in ice-water and gently stirred whilst the arsine–benzene mixture was added during 10—15 minutes, heat being evolved during the reaction. The formation of the arsine–Grignard reagent was completed by 30 minutes' boiling under reflux and then cooling, nitrogen being passed over the mixture throughout. The solution, which was very sensitive to moisture and air, was quite clear but dark in colour. The second reagent was added at this stage. The use of bromobenzene in the formation of the arsine–Grignard reagent always produced a small quantity of diphenyl. If the latter proved difficult to separate from any of the final products, ethyl bromide was used in place of the bromobenzene.

2-Phenylisoarsindoline (II).—(i) A solution of *o*-xylylene dibromide (23·6 g., 1 mol.) in benzene (100 c.c.) was added to the stirred solution of the arsine-Grignard reagent, prepared from phenylarsine (15·3 g., 1 mol.), at such a rate that no appreciable rise in temperature occurred. The complete mixture was then boiled under reflux for 90 minutes, during which fine white crystals separated, and was then cooled in ice-water, whereupon much of the crystalline material redissolved. The solution was then hydrolysed by saturated aqueous ammonium chloride solution, and the pale yellow organic layer was collected, dried, filtered, and distilled under a carbon dioxide atmosphere throughout. The following

fractions were collected at 0·15 mm. : (*a*) b. p. 60—110°, unchanged dibromide (1·8 g.); (*b*) b. p. 110—150°, crude *iso*arsindoline (11·5 g.); (*c*) b. p. 150—175°, also crude *iso*arsindoline (6·3 g.). For characterisation and purification, fractions (*b*) and (*c*) were oxidised to the hydroxynitrate, which was then recrystallised from alcohol (cf. Lyon and Mann, *loc. cit.*) and its identity confirmed by analysis and mixed m.p.s. The yields of the pure salt from (*b*) and (*c*) were 11·4 and 3·9 g., respectively. With allowance for the recovered bromide, the yield of crude *iso*arsindoline is therefore 84% and that of the pure hydroxynitrate is 55·5%.

(ii) The previous experiment was repeated, using however the Grignard reagent from phenylarsine (5·35 g., 1 mol.), and *o*-xylylene dichloride (6 g., 1 mol.). The organic layer was again collected, dried, and filtered, and the solvent then removed. The cold residue consisted of a viscous oil containing a small quantity of crystals. These were collected by hand, washed with alcohol, and recrystallised from alcohol; they had m. p. 181—182°, changed to 181—185° when mixed with an authentic sample of the hydrocarbon (III) of m. p. 188°. Lack of material prevented further recrystallisation. The viscous liquid, when distilled at 0·1 mm., gave the fractions : (*a*) b. p. 70—110° (mainly 75—80°), 1·15 g.; (*b*) b. p. 110—133° (mainly 129—133°), 3·45 g.; (*c*) b. p. 133—145°, 1·15 g. The b. p. and halogen content of fraction (*a*) indicated that it was phenyldichlorarsine. This was confirmed by boiling a sample with an alcoholic solution of piperidine *N*-pentamethylenedithiocarbamate, whereby phenylarsinebis-(*N*-pentamethylenedithiourethane) was deposited, m. p. (after purification) 175—176°, unchanged by admixture with an authentic sample. Fraction (*a*) represents 15% of the phenylarsine taken. Fraction (*b*) was almost pure phenyl*iso*arsindoline (40% yield), whilst (*c*) was less pure material. The two fractions when united and oxidised gave the pure hydroxynitrate, m. p. 148° (alone and mixed) (2·35 g., 20%).

2-*Phenyl*-1 : 2 : 3 : 4-*tetrahydroisoarsindine* (V).—(i) A solution of the dibromide (IV) (8·13 g., 1 mol.) in benzene (40 c.c.) was added to the Grignard reagent prepared from phenylarsine (4·5 g., 1 mol.) and initially at 10°. Heat was evolved during the addition, and the complete mixture was boiled under reflux for 90 minutes, and then cooled and hydrolysed as usual. The organic layer, when distilled at 0·3 mm., gave two main fractions : (*a*) b. p. 73—77° (1·5 g.); (*b*) 140—145° (4·7 g.). Fraction (*a*) contained bromine and was identified as the bromohydrocarbon (VI) by treatment with hot alcoholic piperidine *N*-pentamethylenedithiocarbamate, which gave 5-2-*o*-*tolylethyl*-*N*-*pentamethylenedithiourethane* as colourless crystals, m. p. 99·5—101°, from alcohol (Found : C, 64·5; H, 7·2; N, 4·8. $C_{15}H_{21}NS_2$ requires C, 64·45; H, 7·6; N, 5·0%). An authentic sample of *o*-2-bromoethyltoluene, prepared by the method of Kipping and Wild (*J.*, 1940, 1239) gave the dithiourethane, m. p. 99—100°, unchanged by admixture with the previous sample. Fraction (*b*) consisted of the crude *iso*arsindoline (60%), and was identified by oxidation to the corresponding hydroxynitrate, which after purification had m. p. 146—147° (mixed and unmixed) (Found : C, 51·4; H, 4·4. Calc. for $C_{14}H_{14}O_4NAs$: C, 51·6; H, 4·6%) (3·8 g., 38%).

Repetition of this experiment using an excess of phenylarsine, *i.e.*, the dibromide (14·6 g.) and phenylarsine (9 g., 1·1 mol.), gave arsenobenzene (1·4 g.). The organic layer again furnished fractions (*a*) (2·6 g.) containing the bromohydrocarbon (VI) and (*b*) containing the crude *iso*arsindoline, b. p. 140—150/0·2 mm. (10·2 g., 72%). On redistillation, (*b*) gave the almost pure *iso*arsindoline, b. p. 127—132°/0·1 mm. (7·7 g., 54%).

(ii) A solution of the dibromide (7·05 g.) in benzene (30 c.c.) was added rapidly to a solution of the Grignard reagent prepared from phenylarsine (3·9 g., 1 mol.) and maintained at 70°. Arsenobenzene (0·75 g.) was obtained, and the *iso*arsindoline gave the purified hydroxynitrate (1·7 g., 25%).

(iii) *By decomposition of the arsonium salt.* A mixture of the dibromide (IV) (6·8 g., 1 mol.) and phenyldimethylarsine (4·45 g., 1 mol.), on gentle heating, rapidly formed a glassy mass of the arsonium salt, which was then slowly heated under reflux to 180—260°/17 mm. during 5½ hours. At the higher temperatures, a liquid refluxed in the condenser and a solid separated in the flask. The total product was then distilled at 0·2 mm. and three fractions were collected arbitrarily since no sharp separation was possible : (*a*) b. p. 90—100°, (*b*) b. p. 100—135°, (*c*) b. p. 135—180°. A portion of fraction (*a*) which contained bromine, when oxidised with nitric acid, furnished phenylmethylarsine dihydroxynitrate, $PhMeAs(OH)_2{\cdot}NO_3$, which after crystallisation from alcohol and then from dilute nitric acid gave colourless crystals, m. p. 146° (Found : C, 32·6; H, 3·4; N, 5·4. Calc. for $C_7H_{10}O_5NAs$: C, 31·9; H, 3·8; N, 5·3%). Burrows (*J. Proc. Roy. Soc. New South Wales*, 1935, **68**, 72) gives m. p. 151°. There is little doubt therefore that fraction (*a*) contained crude phenylmethylbromoarsine, although there was insufficient hydroxynitrate for complete purification.

The addition of ether (or benzene) to the remainder of fraction (*a*) and to fractions (*b*) and (*c*) after exposure to damp air precipitated phenyldimethylarsine hydroxybromide, $PhMe_2As(OH)Br$, which when collected and purified by careful precipitation from alcoholic solution by ethyl acetate formed colourless crystals, m. p. 152—153° (Found : C, 34·9; H, 4·4. Calc. for $C_8H_{12}OBrAs$: C, 34·4; H, 4·3%). This compound was converted into the corresponding hydroxypicrate, m. p. 130—131° after recrystallisation from alcohol (Found : C, 39·6; H, 3·7; N, 9·85. Calc. for $C_{14}H_{14}O_8N_3As$: C, 39·3; H, 3·3; N, 9·8%). Steinkopf and Schwen (*Ber.*, 1921, **54**, 2791] give m. p. 162° and 122° respectively for these compounds.

The ether-soluble portions of fractions (*b*) and (*c*) were concentrated and oxidised, 2-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline hydroxynitrate, m. p. 140—141°, being obtained after recrystallisation from alcohol and dilute nitric acid. Its identity was confirmed by mixed m. p., but the yield was very low.

Repetition of this experiment gave an 8% yield of the hydroxynitrate, and it is obvious that the arsonium salt decomposition method, which is so valuable in the *iso*arsindoline series, is not a practicable preparative method in the *iso*arsinoline series.

2-*Iodo*-1 : 2 : 3 : 4-*tetrahydroisoarsindine*.—A mixture of the 2-phenylarsine (V) (1·65 g.) and hydriodic acid of constant b. p. (85 c.c.) was boiled under reflux in a carbon dioxide atmosphere for 2 hours. The cold product was diluted with water and extracted with ether. Removal of the solvent left the 2-iodo-arsine as a red oil which did not solidify. In view of the small quantity available, it was identified by reaction with piperidine *N*-pentamethylenedithiocarbamate in hot alcohol; the solid

derivative, when thrice recrystallised from alcohol and once from *cyclo*hexane, gave *N-pentamethylene-S-2-(1 : 2 : 3 : 4-tetrahydroisoarsinoline)dithiourethane* as colourless crystals, m. p. 121·5—122° (Found: C, 51·55; H, 5·5; N, 4·0. $C_{15}H_{20}NS_2As$ requires C, 51·0; H, 5·7; N, 4·0%).

1 : 8-*Dihydroxymethylnaphthalene* (VII).—Lithium aluminium hydride (9 g., 2·7 equivs.) and ether (280 c.c.) were stirred together in a dry apparatus for several hours to obtain complete dissolution. Powdered methyl naphthalate (21·8 g., 1 equiv.) was placed in an extraction thimble below a reflux condenser fitted to the reaction flask, and the ether boiled gently so that the ester was transferred to the solution during *ca.* 75 minutes. The mixture was cooled to 0°, hydrolysed with 10% sulphuric acid, and filtered. The *diol* (VII), being almost insoluble in ether, was thus collected, and recrystallised from methyl alcohol, forming colourless crystals, m. p. 152—154° (Found: C, 76·5; H, 6·3. $C_{12}H_{12}O_2$ requires C, 76·5; H, 6·4%) (12·1 g., 72%). The above large excess of the hydride was found to be essential in order to avoid contamination of the diol with unchanged ester.

1 : 8-*Bisbromomethylnaphthalene* (VIII).—A mixture of the powdered diol (VII) (13·6 g.) and hot hydrobromic acid of constant b.p. (50 c.c.) was shaken for 45 minutes and then cooled. The solid material which separated was collected and recrystallised from benzene, the *dibromo*-compound (VIII) being thus obtained as large colourless crystals, m. p. 128—129·5° (Found: C, 46·1; H, 3·4. $C_{12}H_{10}Br_2$ requires C, 45·9; H, 3·2%) (5·6 g., 25%).

The benzene mother-liquor was evaporated and the residue, when recrystallised from light petroleum (b. p. 60—80°), furnished well-formed compact crystals of 2-oxaperinaphthane (IX), m. p. 80—81° (Found: C, 84·7; H, 5·8. Calc. for $C_{12}H_{10}O$: C, 84·7; H, 5·9%) (2·8 g., 23%). No ready method for the conversion of this ether into the dibromide (VIII) was found, and the original conversion of the diol (VII) into the dibromide was less satisfactory when acetic acid was used as a solvent.

2-*Phenylarsaperinaphthane* (X; R = Ph).—A solution of the dibromide (VIII) (6 g.) in warm benzene (35 c.c.) was added to an agitated solution of the Grignard reagent prepared as before from phenylarsine (3·1 g.) and maintained at 0°. The complete mixture was boiled under reflux for 1 hour, cooled, and hydrolysed with 10% sulphuric acid. The organic layer was separated from a small quantity of arsenobenzene and dried (Na_2SO_4), and the solvent removed. The pale brown residual gum (3·5 g., 60%) did not boil below 180°/0·1 mm. and could not be obtained crystalline.

When a portion was dissolved in warm methyl iodide, the *methiodide* rapidly crystallised. It was recrystallised from alcohol containing a small proportion of acetone, and separated as a *mono-alcoholate*, m. p. 196—199° in a pre-heated bath (Found: C, 52·95; H, 4·75. $C_{19}H_{18}IAs,C_3H_6O$ requires C, 52·7; H, 5·0%). When this substance was heated at 100°/0·4 mm. for 10 hours, the solvent-free salt, of unchanged m. p., was obtained (Found: C, 51·15; H, 4·0. $C_{19}H_{18}IAs$ requires C, 50·95; H, 4·0%).

An acetone solution of the arsine, when treated with an aqueous-alcoholic solution of potassium palladochloride, readily furnished *dichlorodi-(2-phenylarsaperinaphthane)palladium* as an orange powder insoluble in all common solvents. It was washed with water, acetone, and hot benzene in turn, and was unaffected by being heated to 240° (Found: C, 54·4; H, 4·1. $C_{38}H_{36}Cl_2As_2Pd$ requires C, 54·7; H, 3·8%).

2-*Iodoarsaperinaphthane* (X; R = I).—A mixture of the 2-phenyl derivative and hydriodic acid of constant b. p. was heated at 125° for 90 minutes in a carbon dioxide atmosphere. The cold partly-solid product was washed with water, and then extracted with boiling alcohol, which on cooling deposited pale yellow crystals of the *2-iodo-arsine*, m. p. 117—119° (preliminary softening) (Found: C, 40·45; H, 3·1. $C_{12}H_{11}IAs$ requires C, 40·5; H, 2·8%).

Reaction with Bromoacetonitrile.—A solution of bromoacetonitrile (16·5 g., 1·9 mols.) in benzene (45 c.c.) was added in the usual way to an ice-cold solution of the Grignard reagent prepared from phenylarsine (11·1 g.), much heat being initially evolved. The complete mixture was boiled under reflux for 3 hours, a reddish-brown gummy material being precipitated. Hydrolysis of the cold product, performed as usual with 10% sulphuric acid, did not redissolve the precipitate. The organic layer was worked up as usual, and after removal of the solvent the residue was extracted with acetone, leaving a residue of arsenobenzene, m. p. 213—216° (1·45 g., 13%). The acetone solution, when carefully distilled at 0·5 mm., gave a number of indefinite fractions, all of which were liquid, contained bromine, and did not crystallise or apparently form a methiodide. The presence of phenyldibromoarsine in some of the fractions was proved by conversion into the bisdithiourethane, m. p. 173—174° (mixed and unmixed).

Reaction with Bromoacetone Diethyl Ketal.—This experiment was performed as the previous one, using the ketal (29·8 g., 2 mols.) and phenylarsine (10·9 g.). The acetone extraction afforded arsenobenzene, m. p. 214—215° (6·3 g., 59%). Distillation of the organic liquid again afforded indefinite fractions, one of which was crude phenyldibromoarsine (6·3 g., 28·5%). The latter was identified (*a*) by cautious treatment with a small proportion of piperidine *N*-pentamethylenedithiocarbamate, whereby *phenylbromoarsine-N-pentamethylenedithiourethane*, colourless crystals, m. p. 125—127°, from ethyl acetate (Found: C, 37·25; H, 4·05; N, 3·6. $C_{18}H_{16}NBrS_4As$ requires C, 36·75; H, 3·8; N, 3·6%), was obtained, (*b*) by treatment with a larger proportion of the reagent, whereby the usual bisdithiourethane, m. p. 173—174°, was obtained. The relation between the two products was confirmed by the ready conversion of the first into the second on treatment with the dithiocarbamate.

Reaction with Ethyl Bromoacetate.—The usual method was employed, using ethyl bromoacetate (19·7 g., 2 mols.) and phenylarsine (9·55 g.). Arsenobenzene (3·1 g., 33%) was isolated, and distillation of the liquid organic residue gave the crude arsine contaminated with phenyldibromoarsine, which could not be readily separated by distillation. The crude redistilled arsine, b. p. 137—144°/0·5 mm., when suitably treated with potassium palladobromide, gave *dibromodiphenyl(biscarbethoxymethylarsine)palladium*, orange crystals, m. p. 110—111°, from methyl alcohol (Found: C, 36·85; H, 4·2; Pd, 11·9. $C_{32}H_{38}O_4Br_2As_2Pd$ requires C, 36·6; H, 4·1; Pd, 11·6%). The phenyldibromoarsine was identified in the usual way.

We are greatly indebted to Dr. R. N. Haszeldine for spectroscopic measurements and to the Department of Scientific and Industrial Research for a grant (M. H. B.).

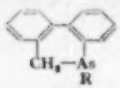
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 30th*, 1950.]

392. *The Synthetic Application of Phenylarsinebis(magnesium Bromide). Part II. The Synthesis and Properties of* 6-*Substituted* 6-*Arsa*-1 : 2 : 3 : 4-*dibenzocyclohepta*-1 : 3-*dienes.*

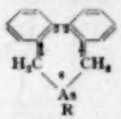
By M. H. Bebby, Frederick G. Mann, and E. E. Turner.

The synthesis of 6-phenyl-6-arsa-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene and its conversion by the action of hydriodic acid into the 6-iodo-analogue are described. The probable dimensions of the central heterocyclic ring in these compounds indicate that the two outer benzene rings are locked at an angle of 63°, and that the compounds therefore possess molecular dissymmetry. This absence of co-planarity of the benzene rings is strongly supported by the spectroscopic evidence.

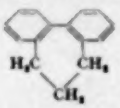
The preparation and properties of 10-substituted 9 : 10-dihydroarsanthridines (I) have recently been recorded by Cookson and Mann (*J.*, 1949, 2888), who showed that a calculation based on accepted bond-lengths and atomic radii indicated that the dimensions of the central heterocyclic ring excluded the possibility of a planar molecule, and that the two benzene rings subtended an angle of *ca.* 34°. On the other hand, the spectroscopic evidence indicated a certain degree of oscillation of the benzene rings about the planar position, since two of these compounds showed an absorption band which was probably the characteristic absorption band of diphenyl slightly displaced and reduced in intensity. The diphenyl band is considered to owe its origin to excited states arising from ionic structures in all of which the two benzene rings of diphenyl are linked by a double bond and are hence coplanar; the reduced intensity of this band in the dihydroarsanthridines would thus imply a certain oscillation about this coplanar position.



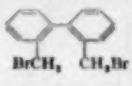
(I.)



(II.)



(III.)

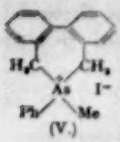


(IV.)

In view of these results, considerable interest attached to compounds of type (II), in which the heterocyclic ring has been increased by the addition of another CH_2 group; such compounds can be regarded systematically as derivatives of 1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene (III), and hence are termed 6-substituted 6-arsa-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-dienes. The ready preparation of 2 : 2′-bisbromomethyldiphenyl (IV) by the method of Hall, Leslie, and Turner (*J.*, 1950, 711) provides a simple approach to compounds of type (II), for we find that the dibromo-compound (IV) reacts smoothly with phenylarsinebis(magnesium bromide) to give 6-phenyl-6-arsa-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene (II; R = Ph), a crystalline compound of m. p. 118—118·5°, and also phenyldibromoarsine as a by-product. The former compound is the first to be isolated having a seven-membered ring consisting solely of carbon and one arsenic atom, although compounds containing a seven-membered ring consisting of carbon and two arsenic atoms are known (Glauert and Mann, *J.*, 1950, 682). The heterocyclic ring in the 6-phenyl compound (II; R = Ph) has however considerable stability, because treatment with boiling hydriodic acid replaces the phenyl group by an iodo-group without affecting the ring, and thus gives 6-iodo-6-arsa-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene, pale yellow crystals, m. p. 117—117·5°. Further action by a Grignard agent would clearly in turn replace the iodo-group with any desired alkyl or aryl group. This fission of a phenyl group directly attached to an arsenic atom which is part of a ring system, without injury to the system itself, appears to be widespread: it has already been shown to occur in the *iso*arsindolines, the 1 : 2 : 3 : 4-tetrahydro*iso*arsinolines, and the 2-arsaperinaphthanes (*J.*, 1947, 662; 1950, 1917).

A study of the stereochemistry of molecules of type (II) reveals several points of interest. If the bond-lengths and the atomic radii utilised by Cookson and Mann (*loc. cit.*) are applied to the tricyclic ring system (II), and an intervalency angle of 100° at the arsenic atom is accepted (cf. Chatt and Mann, *J.*, 1940, 1184), calculation shows that the two benzene rings subtend an angle of 63°; moreover the intervalency angle within the ring at carbon atoms 5 and 7 becomes 110°, and the ring is presumably almost strainless. A model based on these dimensions

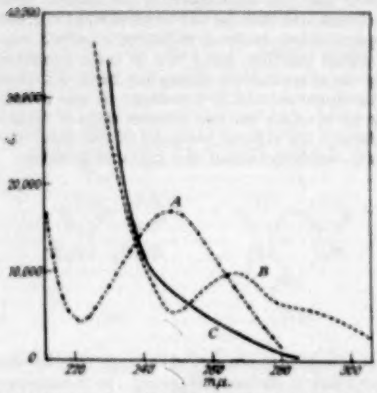
shows that the central heterocyclic ring locks the two non-planar benzene rings in position, and that no rotation of them about their common axis is possible. When the tertiary arsine forms a quaternary salt, *e.g.*, the monomethiodide of 6-phenyl-6-arsa-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene (alternatively named 6-phenyl-6-methyl-6-arsonia-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene iodide) (V), the intervalency angle within the ring of the arsenic atom almost certainly increases to *ca.* 109°; since however there will be a simultaneous shrinkage of the interatomic As–C distance, the process will probably be without notable effect on the angle between the two benzene rings and on the stability of the heterocyclic ring.



(V.)

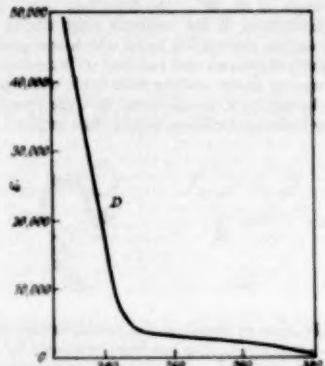
Spectroscopic evidence confirms these considerations. In Fig. 1 there are shown for comparative purposes: the absorption spectrum of diphenyl (*A*), having the characteristic band at 248 mμ., $\varepsilon_{max.}$ 17,000, due to the coplanar rings; the spectrum of 10-phenyl-10-methyl-9 : 10-dihydroarsanthridinium iodide (*B*), having the band at 269 mμ., $\varepsilon_{max.}$ 9,600 (Cookson and Mann, *loc. cit.*); and the spectrum of 6-phenyl-6-methyl-6-arsonia-1 : 2 : 3 : 4-dibenz*cyclo*-

Fig. 1.



(*A*) *Diphenyl.* (*B*) *10-Phenyl-10-methyl-9 : 10-dihydroarsanthridinium iodide.* (*C*) *6-Phenyl-6-methyl-6-arsonia-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene iodide.*

Fig. 2.



*6-Iodo-6-arsa-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene.*

hepta-1 : 3-diene iodide (V) (*C*), in which this band is entirely absent. Fig. 2 gives the absorption spectrum of the 6-iodo-derivative (II; R = I); this also shows no sign of the diphenyl band, and the absence of rotation about the common axis of the two benzene rings in those compounds is thus strikingly confirmed. It is noteworthy that the spectra of the quaternary methiodide (V) and the 6-iodo-compound (II; R = I) although closely similar are not identical, wherein they differ from those of the analogous derivatives in the 2-arsaperinaphthane series, which are almost completely identical (cf. previous paper).

The twisted heterocyclic ring in compounds of type (II) causes these tertiary arsines to possess molecular dissymmetry: the formation of a quaternary salt such as (V), having two dissimilar groups joined to the arsenic atom, does not produce an asymmetric arsenic atom, but the molecular dissymmetry of course persists. Such compounds should therefore be resolvable into optically active forms, a possibility which is now being investigated.

Experimental.

*6-Phenyl-6-arsa-1 : 2 : 3 : 4-dibenz*cyclo*hepta-1 : 3-diene* (II; R = Ph).—A solution of 2 : 2'-bisbromomethyldiphenyl (IV) (8 g.) in benzene (30 c.c.) was added to the chilled and agitated ether–benzene solution of the arsine-Grignard reagent prepared from phenylarsine (3·65 g., 1 mol.) (see preceding paper). The complete mixture was stirred at room temperature for 30 minutes and then boiled under reflux for 1 hour. After cooling and hydrolysis with ammonium chloride solution, the organic layer was separated, dried, and evaporated. The semi-solid residue, when recrystallised from alcohol, gave the *arsine* (II; R = Ph) (3·55 g., 45%), m. p. 112—115°, increased to 118—118·5° by further recrystallisation (Found:

C, 71·6; H, 5·2; *M*, ebullioscopic in 1·486% alcoholic solution, 342. $C_{30}H_{31}As$ requires C, 72·3; H, 5·2%; *M*, 332). The alcoholic mother-liquor contained phenyldibromoarsine, for when treated with piperidine *N*-pentamethylenedithiocarbamate it deposited phenylarsinebis-(*N*-pentamethylenedithiourethane), which after purification had m. p. 175—176°, unchanged by admixture with an authentic sample.

A mixture of the arsine and methyl iodide was boiled under reflux for 30 minutes and then evaporated. Recrystallisation of the residue from methyl alcohol gave *6-phenyl-6-methyl-6-arsonia-1 : 2 : 3 : 4-dibenzocyclohepta-1 : 3-diene iodide* (V) as a *monomethanolate* which on heating lost methyl alcohol at *ca.* 104° (Found : C, 51·9; H, 4·8. $C_{31}H_{30}IAs,CH_4O$ requires C, 52·2; H, 4·8%). After 2 hours' heating at 128°/0·1 mm. the solvent-free iodide, m. p. 223—224° (preliminary darkening) was obtained (Found : C, 53·15; H, 4·3. $C_{31}H_{30}IAs$ requires C, 53·2; H, 4·25%).

When a benzene solution containing equimolecular quantities of the arsine and *p*-chlorophenacyl bromide was boiled under reflux for 1 hour and cooled, colourless crystals of *6-phenyl-6-p-chlorophenacyl-6-arsonia-1 : 2 : 3 : 4-dibenzocyclohepta-1 : 3-diene bromide* separated. Recrystallisation from alcohol–benzene gave crystals which retained benzene even when heated at 60°/0·1 mm. for 2 hours; heating at 100°/0·1 mm. for 3 hours ultimately gave the solvent-free but rather glassy bromide, m. p. *ca.* 110—115° (Found : C, 59·0; H, 4·0. $C_{34}H_{26}OClBrAs$ requires C, 59·4; H, 4·1%).

A mixture of the arsine and hydriodic acid of constant b. p. was boiled under reflux for 2 hours in a carbon dioxide atmosphere. The liquid was decanted from the cold product, and the solid residue, when washed with water and recrystallised first from alcohol and then from light petroleum (b. p. 80—100°), gave *6-iodo-6-arsa-1 : 2 : 3 : 4-dibenzocyclohepta-1 : 3-diene* (II; R = I) as yellow crystals, m. p. 117—117·5° (Found : C, 44·2; H, 3·2. $C_{19}H_{14}IAs$ requires C, 44·0; H, 3·2%).

We are greatly indebted to Dr. D. M. Hall for a gift of 2 : 2'-bisbromomethyldiphenyl, to Dr. R. N. Haszeldine for spectroscopic measurements, and to the Department of Scientific and Industrial Research for a grant (M. H. B.).

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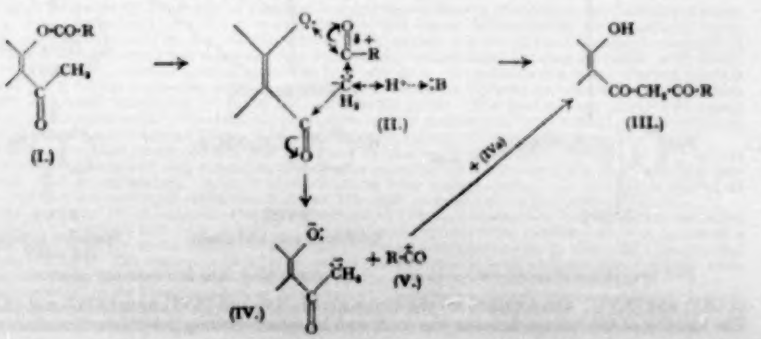
393. *Further Experiments on the Mechanism of the Baker–Venkataraman Transformation.*

By J. E. GOWAN and T. S. WHEELER.

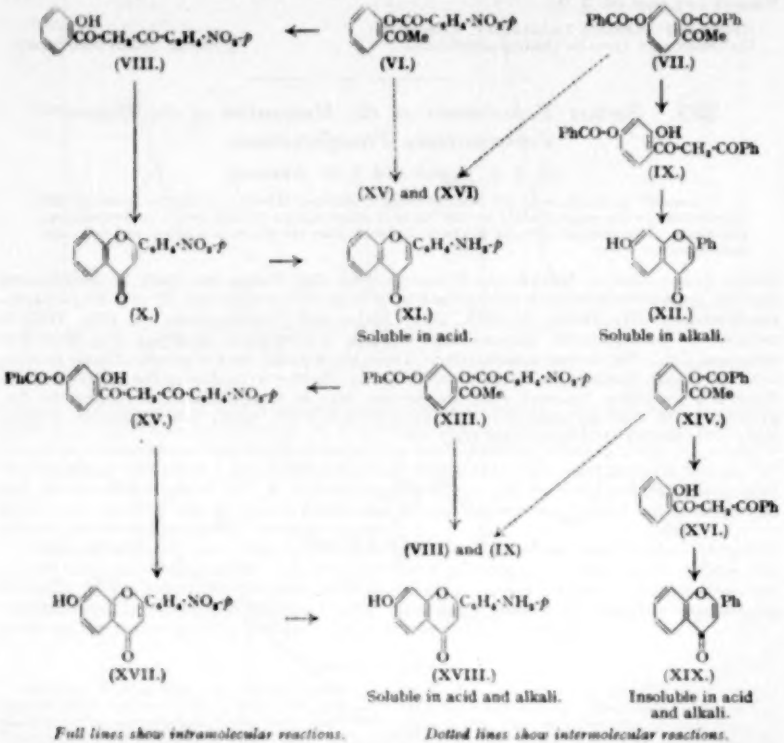
"Crossed" products were not isolated when a mixture of two *o*-aroyloxyacetoarones was transformed in the same solution by the Baker–Venkataraman method into *o*-hydroxydiaroylmethanes. The absence of these products indicates that the reaction is intra- and not intermolecular.

DOYLE, GÓGAN, GOWAN, KEANE, AND WHEELER (*Proc. Roy. Dublin Soc.*, 1948, **24**, 291) showed that the Baker–Venkataraman transformation of *o*-aroyloxyacetoarones (I) into *o*-hydroxydiaroylmethanes (III) (Baker, *J.*, 1933, 1381; Mahal and Venkataraman, *J.*, 1934, 1767) is probably a base-catalysed intramolecular Claisen condensation involving the transition compound (II). The nature of the catalysis is scarcely in doubt since a variety of bases ranging from the triphenylmethyl ion to the benzoate ion is effective in producing the rearrangement. There is a possibility, however, that the reaction may be intermolecular, involving the dissociation of (II) into the anion (IV) and the aroyl cation (V), which latter condenses with an anion (IVa) similar to (IV), to form (III).



This paper describes experiments, the results of which indicate that the reaction is intramolecular and (V) is never free during rearrangement. The method employed is that used by Ingold and Kidd (*J.*, 1933, 984) in an investigation of the mechanism of the benzidine change. A mixture of *o*-(*p*-nitrobenzoyloxy)acetophenone (VI) and of 2 : 4-dibenzoyloxyacetophenone (VII) was transformed in pyridine solution by using powdered potassium hydroxide. The resulting diketone mixture was cyclized to the corresponding flavones with concentrated sulphuric acid which simultaneously hydrolyses any aroyloxy-groups present (Baker, *loc. cit.*), and the product was treated with stannous chloride in hydrochloric acid to convert any nitro-flavone formed into the corresponding amino-flavone.

If the reaction is intramolecular, (VI) will give (XI) with intermediate formation of (VIII) and (X), and (VII) will yield similarly (IX) and thence (XII). On the other hand, if aroyl ions become free during the transformation, (XV) and (XVI) will also be formed. Compound (XV) will produce (XVII) and thence (XVIII), and (XVI) will give (XIX). The four flavones (XI), (XII), (XVIII), and (XIX) can be separated by suitable treatment with acid and alkali; this was confirmed by starting with a mixture of (X), (XII), (XVII), and (XIX) which was reduced and separated. As shown in the Experimental section, a mixture of (VI) and (VII) gave (XI) and (XII) only, and a mixture of (XIII) and (XIV) yielded exclusively (XVIII) and (XIX). The fact that each mixture gave " straight " as opposed to " crossed " products indicates that the formation of (VIII) and (IX) only from (VI) and (VII) is not due to the complete instability



of (XV) and (XVI); and similarly for the formation of (XV) and (XVI) from (XIII) and (XIV). The identity of the various flavones was confirmed by mixed-melting-point determinations with

authentic specimens. In the synthesis of these specimens no striking difference was observed in the rate of transformation of the four esters (VI, VII, XIII, and XIV) involved. If one ester of a pair in a mixture transformed much more rapidly than the other, it might be that all the corresponding free aroyl ion (IV), if formed, would have recombined to form the straight diketone before the slow transformation of the second ester would have sensibly progressed (see Ingold and Kidd, *loc. cit.*).

As there is a loss in the various stages of transformation, cyclization and reduction, and, as the control experiments show, in the separation of the flavones produced, it is not possible to assert that no intermolecular exchange occurs. The evidence, however, is in favour of intramolecular reaction, and it is probable that the transformation proceeds exclusively in this way.

Experimental.

4-Benzoyloxy-2-(p-nitrobenzoyloxy)acetophenone (XIII) separated when a mixture of 2-hydroxy-4-benzoyloxyacetophenone (10·8 g.) (Baker, *J.*, 1933, 1381), *p*-nitrobenzoyl chloride (8·8 g.), and pyridine (30 ml.), which had been heated for 3 hours at 100°, was poured into excess of 10% hydrochloric acid. The *ester* which was recovered after the product had been kept overnight at 0° yielded on extraction with boiling methyl alcohol (4 × 150 ml.) white needles (12·8 g., 75%) which melted at 110—112° (Found: C, 64·7; H, 3·8; N, 3·4. $C_{22}H_{15}O_7N$ requires C, 65·2; H, 3·7; N, 3·5%).

4′-Nitro-2-hydroxy-4-benzoyloxydibenzoylmethane (XV).—A mixture of 4-benzoyloxy-2-(*p*-nitrobenzoyloxy)acetophenone (2 g.), pyridine (20 ml.), and potassium hydroxide (1 g.), previously powdered in a hot mortar, was heated for 15 minutes under reflux, a copious precipitate of the yellow potassium salt of 4′-nitro-2-hydroxy-4-benzoyloxydibenzoylmethane being obtained. The product was poured into excess of 10% acetic acid and the resulting *phenol* (1·3 g., 65%) was twice crystallized from acetone–dioxan (charcoal). It separated in yellow crystals, m. p. 198—200° (Found: C, 65·4; H, 3·7; N, 3·6. $C_{22}H_{15}O_7N$ requires C, 65·2; H, 3·7; N, 3·5%).

2-Hydroxy-4-benzoyloxydibenzoylmethane (IX) was similarly prepared (50% yield) from 2 : 4-dibenzoyloxyacetophenone (VII) (Baker, *loc. cit.*), and 4′-nitro-2-hydroxydibenzoylmethane (VIII) (90% yield) from *o*-(*p*-nitrobenzoyloxy)acetophenone (VI) (Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291).

Preparation of Authentic Specimens of Flavones.—4′-Nitro-2-hydroxy-4-benzoyloxydibenzoylmethane was dissolved in concentrated sulphuric acid (cf. Baker, *loc. cit.*) and after 4 hours the solution was poured with cooling into excess of water. The resulting precipitate of 4′-nitro-7-hydroxyflavone (XVII) separated from glacial acetic acid in light yellow crystals (92%) which melted at 308—310°. Anand and Venkataraman (*Proc. Indian Acad. Sci.*, 1947, **26**, 279) give m. p. 310—311°.

7-Hydroxyflavone (XII) was similarly obtained (96% yield) from 2-hydroxy-4-benzoyloxydibenzoylmethane and was conveniently purified through the acetyl derivative (Emilewicz and Kostanecki, *Ber.*, 1898, **31**, 704). 4′-Nitroflavone (X) was prepared (91% yield) from 4′-nitro-2-hydroxydibenzoylmethane by using acetic acid containing a trace of mineral acid as described by Doyle *et al.* (*loc. cit.*). Flavone (XIX) was synthesized by the Baker–Venkataraman method from *o*-benzoyloxyacetophenone in over 70% yield (see Dunne *et al.*, *J.*, 1950, 1252).

4′-Amino-7-hydroxyflavone (XVIII).—A mixture of 4′-nitro-7-hydroxyflavone (0·3 g.), stannous chloride (1·5 g.), and concentrated hydrochloric acid (10 ml.) was heated for 30 minutes under reflux. The precipitate obtained on keeping the product for some hours at 0° was dissolved in methyl alcohol, and the solution was made strongly alkaline by the drop-wise addition of aqueous ammonia (*d* 0·880) and concentrated at 100°. The yellow crystals (0·1 g., 37%) which separated melted at 337—338° after crystallization from methyl alcohol. Anand and Venkataraman (*loc. cit.*) give m. p. 338—340°.

4′-Aminoflavone (XI) was similarly obtained from 4′-nitroflavone by using 20% sodium hydroxide solution to precipitate the base from the solution of the hydrochloride (cf. Doyle *et al.*, *loc. cit.*, p. 304). The product separated from alcohol in yellow needles (86%) which melted at 233—234°. Bogert and Marcus (*J. Amer. Chem. Soc.*, 1919, **41**, 92) give m. p. 234—236°.

Test of Technique for Separation of Flavones.—A mixture of flavone, 4′-nitroflavone, 7-hydroxyflavone and 4′-nitro-7-hydroxyflavone (0·5 g. of each flavone) was heated intermittently for 15 minutes under reflux with stannous chloride (5 g.) in concentrated hydrochloric acid (15 ml.) and then kept overnight at 0°. The solid (*A*) formed was separated and treated with concentrated aqueous ammonia, with water, and then with 10% aqueous sodium hydroxide (2 × 100 ml.). On acidification of the alkaline solution beyond pH 1, 7-hydroxyflavone (0·39 g.) separated (*B*). It was acetylated by treatment for 15 minutes at 100° with acetic anhydride (10 parts) and pyridine (10 parts). The product was poured into excess of 10% hydrochloric acid. The resulting precipitate after crystallization from methyl alcohol melted at 129—130° and did not depress the m. p. of an authentic specimen of 7-acetoxyflavone.

The acid mother-liquor (*B*) did not yield any further solid when kept overnight at 0°. It was neutralized to Congo-red with concentrated aqueous ammonia and kept overnight at 0°, a yellow precipitate (0·12 g.) separating. After 2 crystallizations from methyl alcohol this precipitate melted at 330—335°; 4′-amino-7-hydroxyflavone melts at 338—340° (Anand and Venkataraman, *loc. cit.*).

The portion of (*A*) (see above), which was insoluble in 10% aqueous sodium hydroxide, was extracted with 5% hydrochloric acid (2 × 100 ml.). The combined extracts when rendered alkaline deposited a yellow solid (0·18 g.) which melted at 228—229°. 4′-Aminoflavone has m. p. 234—236° (Bogert and Marcus, *loc. cit.*). The residue (0·45 g.) of (*A*) which was insoluble in both acid and alkali yielded, when crystallized from light petroleum (b. p. 40—60°), flavone with m. p. 97° (lit., m. p. 99—100°).

Experiments on the Transformation of Mixtures.—(1) *Simultaneous transformation of o-(p-nitrobenzoyloxy)acetophenone* (VI) *and 2 : 4-dibenzoyloxyacetophenone* (VII). A mixture of *o*-(*p*-nitrobenzoyloxy)-acetophenone (1 g.), 2 : 4-dibenzoyloxyacetophenone (1 g.), powdered potassium hydroxide (1 g.), and

pyridine (25 ml.) was heated for 30 minutes under reflux, and when cool was diluted with water (250 ml.) and acidified with glacial acetic acid. The insoluble yellow solid so obtained was collected, dried, and dissolved in concentrated sulphuric acid (25 ml.). After 4 hours the solution was added with cooling to water (300 ml.). The resulting buff-coloured precipitate was dried at 100° and heated intermittently under reflux for 30 minutes with stannous chloride (5 g.) in concentrated hydrochloric acid (15 ml.). The solid which separated after the mixture had been kept overnight at 0° was treated with concentrated aqueous ammonia, washed with water, and dried. It was ground and extracted with 10% aqueous sodium hydroxide (2 × 50 ml.) (*C*) and the combined extracts acidified with concentrated hydrochloric acid (*D*). The resulting precipitate (0·27 g.) was acetylated as described above for 7-hydroxyflavone (XII). The product after crystallization from methyl alcohol melted at 129° and did not depress the m. p. of an authentic specimen of 7-acetoxyflavone.

The acid mother-liquor [see (*D*) above] was neutralized to Congo-red with concentrated aqueous ammonia but yielded no precipitate when kept overnight at 0° [absence of 4′-amino-7-hydroxyflavone (XVIII)].

The residue from the alkaline extraction [see (*C*) above] dissolved completely in 10% hydrochloric acid (50 ml.) [absence of flavone (XIX)], and this acid extract on treatment with 10% aqueous potassium hydroxide to alkalinity gave a yellow solid (0·11 g.) which after crystallization from alcohol melted at 231° and did not depress the m. p. of an authentic specimen of 4′-aminoflavone (XI).

(2) *Simultaneous transformation of o-benzoyloxyacetophenone* (XIV) and *4-benzoyloxy-2-(p-nitrobenzoyloxy)acetophenone* (XIII). A mixture of *o*-benzoyloxyacetophenone (1 g.) and 4-benzoyloxy-2-(*p*-nitrobenzoyloxy)acetophenone (1 g.), potassium hydroxide (1 g.), and pyridine (25 ml.) was heated under reflux and treated as described at (1) above up to and including reduction with stannous chloride in hydrochloric acid and subsequent treatment with aqueous ammonia and with water. The dried solid product was extracted with 10% aqueous sodium hydroxide (*E*). On acidification of the extract with concentrated hydrochloric acid a transient opalescence but no permanent precipitate was obtained [absence of 7-hydroxyflavone (XII)]. The acidified extract was neutralized to Congo-red with concentrated aqueous ammonia and kept overnight at 0°. The crude yellow solid (0·09 g.) melted at 300—320° and this m. p. was raised to 323—330° by addition of an authentic sample of 4′-amino-7-hydroxyflavone, (XVIII).

The residue [see (*E*) above] which was insoluble in alkali was extracted with 10% hydrochloric acid (2 × 50 ml.), but no precipitate was obtained when this extract was rendered alkaline with 10% aqueous potassium hydroxide [absence of 4′-aminoflavone (XI)]. The solid remaining after the alkali and the acid extraction was crystallized from light petroleum (b. p. 40—60°), whereupon it melted at 97° and did not depress the m. p. of an authentic sample of flavone (XIX).

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UNIVERSITY COLLEGE, DUBLIN. [*Received, April 17th*, 1950.]

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394. *The Heats of Hydrolysis of Chloral and Bromal, and the C—C Bond Dissociation Energies in Chloral and Bromal.*

By H. O. PRITCHARD and H. A. SKINNER.

From measurements of the heats of reaction of liquid chloral and bromal with aqueous sodium hydroxide at room temperature, the following values (kcals. mole^{-1}) were obtained for the heats of formation: $Q_f(Cl_3C\cdot CHO,liq.) = 82{\cdot}1$, $Q_f(Br_3C\cdot CHO,liq.) = (x + 20{\cdot}7)$, where x is the heat of formation of liquid bromoform. An estimate of x as 0·5 kcal. is given, corresponding to $Q_f(Br_3C\cdot CHO,liq.) = 21{\cdot}2$ kcals. mole^{-1}.

The C–C bond dissociation energy in chloral is calculated at 62 kcals. mole^{-1}, and a similar value is found for C–C in bromal on the assumption that the C–H dissociation energies are the same in bromoform as in chloroform.

BOTH chloral and bromal react readily at room temperature with aqueous alkalis, according to the equation:

$$X_3C\cdot CHO + NaOH(aq.) \longrightarrow X_3CH + H\cdot CO_2Na(aq.) \quad . \quad . \quad . \quad . \quad (1)$$
$$(X = Cl \text{ or } Br)$$

From the measured heat of reaction (1), it is possible to derive the heat of formation, $Q_f(X_3C\cdot CHO)$, of $X_3C\cdot CHO$. By combining the $Q_f(X_3C\cdot CHO)$ values with other thermal data, the heats of dissociation of the C–C bonds in these compounds can be derived.

The heat of reaction of liquid chloral with aqueous potassium hydroxide was first measured some 70 years ago by Berthelot (*Ann. Chim. Phys.*, 1877, **12**, 536; 1880, **20**, 521), whose results agree substantially with those given in this paper. No previous measurements of the heat of hydrolysis of bromal have been reported.

EXPERIMENTAL.

Preparations.—Chloral (anhydrous) (a B.D.H. product) was purified by careful fractionation in a steel-gauze-packed column, dried by distillation over phosphoric oxide, and re-distilled through an

efficient packed column; it then had b. p. 97·7—98°/766 mm. The pure product was distilled *in vacuo* and collected in weighed glass ampoules.

The bromal (anhydrous) (a B.D.H. sample) was purified by careful fractionation at 8—9 mm. The early fractions containing hydrogen bromide as impurity were discarded, and the pure, almost colourless product was collected in weighed glass ampoules.

The formic acid and sodium hydroxide were of analytical quality.

Calorimeter.—The reactions were carried out by breaking the glass ampoules into an excess (750 c.c.) of 0·2*x*-sodium hydroxide. The reaction vessel was a Dewar flask, and the calorimetric system was that described by Pritchard and Skinner (*J.*, 1950, 272). The temperature changes were recorded in terms of the resistance changes of a thermistor element (R_i = initial and R_f = final resistance of the thermistor element).

Results.

Chloral.—The results obtained from 4 measurements of the heat of reaction ($Q_{obs.}$) of liquid chloral with aqueous sodium hydroxide are listed in Table I. In the final column of this table, calculated values of Q_f($Cl_3C{\cdot}CHO$,liq.) are given, which were obtained from the equation:

$$Q_f(Cl_3C{\cdot}CHO,liq.) = Q_f(H{\cdot}CO_2Na,aq.) + Q_f(Cl_3CH,aq.) - Q_f(NaOH,aq.) - Q_{obs.} \quad . \quad . \quad (2)$$

The terms in Q_f appearing on the right-hand side of equation (2) were assumed to have the following values:

$$Q_f(NaOH,\ 275\ H_2O) = 112{\cdot}06 \text{ kcals. mole}^{-1}$$
$$Q_f(H{\cdot}CO_2Na,aq.) = 155{\cdot}12 \quad ,,$$
$$Q_f(Cl_3CH,aq.) = 33{\cdot}67 \quad ,,$$

The value for Q_f(NaOH,aq.) is that given by Bichowsky and Rossini ("Thermochemistry of Chemical Substances," Reinhold, 1936), and that for $Q_f(H{\cdot}CO_2Na,aq.)$ we obtained by direct measurement of the heat of neutralization of formic acid in an excess of sodium hydroxide, coupled with an assumed value for the heat of formation of formic acid ("Selected Values of Chemical Thermodynamic Properties," Table 23—4, Nat. Bur. Standards, Washington). Under the conditions of our experiments, the chloroform was formed in aqueous solution, so that the appropriate Q_f value required in equation (2) is that for dissolved Cl_3CH. Berthelot (*loc. cit.*) measured the heat of solution of liquid chloroform in water as 2·17 kcals. mole^{-1}, which, combined with the value $Q_f(Cl_3CH,liq.)$ = 31·5 kcals. mole^{-1} [Nat. Bur. Standards, Table 23—7], leads to $Q_f(Cl_3CH,aq.)$ = 33·67 kcals. mole^{-1}. It should be pointed out, however, that the heat of formation of chloroform is not known with high precision, and an error of the order of ±1 kcal. is associated with the value we have used.

Table I.

Chloral and aqueous sodium hydroxide.

Expt.	$Cl_3C{\cdot}CHO$ (g.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	Q_f ($Cl_3C{\cdot}CHO$, liq.) (kcals.).
1	3·0156	1728·2$_5$	1685·0	24·57	52·16
2	2·8556	1716·0	1675·2	24·63	52·10
3	3·0944	1738·8$_5$	1694·4	24·54	52·19
4	3·1626	1738·4	1692·8	24·57	52·16
			Mean	24·58	52·13

Table II.

Bromal and aqueous sodium hydroxide.

Expt.	$Br_3C{\cdot}CHO$ (g.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	Q_f ($Br_3C{\cdot}CHO$, liq.) (kcals.).
1	4·8475	1736·8	1703·3	22·38	x + 20·68
2	4·4810	1731·6	1700·5	22·44	x + 20·62
3	5·0530	1751·2	1709·8	22·38	x + 20·68
			Mean	22·40	x + 20·66

Bromal.—The results obtained from 3 representative reactions of bromal with sodium hydroxide are summarised in Table II. The values of the heat of formation of liquid bromal are given in terms of a quantity x, which is the heat of formation of liquid bromoform. The value of $Q_f(Br_3CH,liq.)$ is not known with any certainty at present. In view of the insolubility of bromoform in water, correction for the solution heat in this case was not considered necessary.

Bichowsky and Rossini (*op. cit.*) estimated $Q_f(Br_3CH,\ g.)$ as −6 kcals. mole^{-1}, but gave no indication of the method by which their estimate was made. We are inclined towards a slightly different estimate, based on an argument of analogy with the case of the chloromethanes. The

heats of formation of the chloromethanes are (Nat. Bur. Standards, Washington, Table 23—7, 1949):

	Q_f (kcals. mole^{-1}).	Δ_1.	Δ_2.
CH_4 (g.)	17·9	1·7	
CH_3Cl (g.)	19·6	1·4	−0·3
CH_2Cl_2 (g.)	21	3·0	1·6
$CHCl_3$ (g.)	24	1·5	−1·5
CCl_4 (g.)	25·5		

First and second differences are listed under Δ_1 and Δ_2. If we now *assume* that the second differences column (Δ_2) is the same in the bromo- as in the chloro-methanes, we obtain the following (estimated Q_f values marked •):

	Q_f (kcals. mole^{-1}).	Δ_1.	Δ_2.
CH_4 (g.)	17·9	−9·3	
CH_3Br (g.)	8·6	−9·6	−0·3
CH_2Br_2 (g.)	−1·0 •	−8·0	1·6
$CHBr_3$ (g.)	−9·0 •	−9·5	−1·5
CBr_4 (g.)	−18·5 •		

This estimate of $Q_f(Br_3CH, g.) = -9$ kcals. mole^{-1} corresponds to a value of *ca.* $+\frac{1}{2}$ kcal. mole^{-1} for the heat of formation of liquid bromoform, so that $x = 0{\cdot}5$ kcal. and $Q_f(Br_3C{\cdot}CHO,liq.)$ is approximately 21·2 kcals. mole^{-1}.

Discussion.

Knowledge of the Q_f values in chloral and bromal, combined with other thermal data, enables us to evaluate the energies of dissociation of the C–C bonds in these compounds. If the heat required to rupture the bond $X_3C{-}CHO$ is represented by $D(X_3C{-}CHO)$, the relevant thermal equation may be written as:

$$D(X_3C{-}CHO) = Q_f(X_3C{\cdot}CHO,g.) - Q_f(X_3C{\cdot}, g.) - Q_f(CHO, g.) \quad . \quad . \quad . \quad (3)$$

The terms in Q_f on the right-hand side of equation (3) are discussed separately below.

$Q_f(X_3C{\cdot}CHO, g.)$. These differ from the heats of formation in the liquid state by the latent heats of vaporization, $\lambda_{vap.}$. Berthelot (*loc. cit.*) measured $\lambda_{vap.}$ ($Cl_3C{\cdot}CHO$) as 8·1 kcals. mole^{-1}, and, although a direct measurement of $\lambda_{vap.}$ for bromal has not been reported, this can be estimated as 9·8 kcals. mole^{-1} with little likelihood of serious error. Using these values for $\lambda_{vap.}$, we obtain $Q_f(Cl_3C{\cdot}CHO, g.) = 44{\cdot}0$, and $Q_f(Br_3C{\cdot}CHO, g.) = 11{\cdot}4$ kcals. mole^{-1}.

$Q_f(X_3C{\cdot}, g.)$. The heat of formation of the $\cdot CCl_3$ radical can be derived from two independent sources. From studies of the photochemical bromination of chloroform, Braunwarth and Schumacher (*Kolloid Z.*, 1939, **89**, 184) obtained values for the energies of activation, E_a, of the forward and reverse reactions:

$$\text{(i)}\ Cl_3CH + Br \longrightarrow {\cdot}CCl_3 + HBr \quad (E_a = 10 \text{ kcals.})$$

$$\text{(ii)}\ {\cdot}CCl_3 + HBr \longrightarrow Cl_3CH + Br \quad (E_a = 6 \text{ kcals.})$$

from which it follows that the heat evolved in reaction (i) is −4 kcals. [i.e., E_a(ii) − E_a(i)]. Since the heat of reaction is numerically equal to the difference in the sums of the heats of formation of products and reactants, we may write:

$$-4 = Q_f(Cl_3C{\cdot}) + Q_f(HBr) - Q_f(Br) - Q_f(CHCl_3) \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

By use of the values (Nat. Bur. Standards, Washington, Tables 11—1, 11—2, 1948) $Q_f(Br) = -26{\cdot}71$ and $Q_f(HBr) = 8{\cdot}66$, with $Q_f(CHCl_3, g.) = 24$ kcals., equation (4) yields $Q_f(Cl_3C{\cdot}) = -15{\cdot}4$ kcals. mole^{-1}.

A check on this value is provided by the experiments of Miller and Willard (Abstracts 116th Meeting, Amer. Chem. Soc., 1949) on the reaction of bromine with carbon tetrachloride. These investigators found that chlorine accelerates the bromination reaction, and suggest that this is because $\cdot CCl_3$ radicals can be formed more easily by the reaction $Cl + CCl_4 \longrightarrow {\cdot}CCl_3 + Cl_2$ than by the reaction $Br + CCl_4 \longrightarrow {\cdot}CCl_3 + BrCl$. Their results indicated an activation energy of 18 kcals. mole^{-1} for the bromine-atom reaction, and 12 kcals. mole^{-1} for the chlorine-atom reaction with carbon tetrachloride. In these reactions the activation energies set an upper limit to the endothermicity of the reactions, so that we may write:

$$\text{(iii)}\ Cl + CCl_4 \longrightarrow {\cdot}CCl_3 + Cl_2 - {<}12 \text{ kcals.}$$

$$\text{(iv)}\ Br + CCl_4 \longrightarrow {\cdot}CCl_3 + BrCl - {<}18 \text{ kcals.}$$

From the heats of these reactions, and known values for the heats of formation of Cl, Br, BrCl, and CCl_4, it follows that $Q_f(\cdot CCl_3) = -{<}15{\cdot}5$ kcals. mole^{-1}.

There are no experimental data at present from which a value for $Q_f(\cdot CBr_3)$ can be deduced. However, if we make the reasonable assumption that the C–H bond dissociation energy in bromoform is the same as that in chloroform [*i.e.*, $D(H{-}CBr_3) = D(H{-}CCl_3) = 91{\cdot}4$ kcals.], we arrive at $Q_f(\cdot CBr_3) = -48{\cdot}4$ kcals.

$Q_f(\cdot CHO, g)$. Roberts and Skinner (*Trans. Faraday Soc.*, **1949**, **45**, 339) have suggested, for the heat of formation of the formyl radical, a value of 0·4 kcal., which they obtained on the assumption that the activation energy of 26 kcals. for the reaction $HCO \longrightarrow H + CO$ measured by Gorin (*J. Chem. Physics*, **1939**, **7**, 256) is equivalent to the heat of the reaction. It has been pointed out to us by Dr. M. Szwarc that the reverse reaction, $H + CO \longrightarrow \cdot CHO$, probably requires a small activation energy, in which case the heat of the forward reaction will be slightly less than the 26 kcals. assumed by Roberts and Skinner. It seems unlikely that the reverse reaction requires an activation energy of more than a few kcals., by analogy with the similar reactions $H + O_2 \longrightarrow HO_2\cdot$ (Bodenstein and Schenk, *Z. physikal. Chem.*, **1933**, **20**, *B*, 420: activation energy, *ca.* 1·5 kcals.) and $H + CH{\equiv}CH_2 \longrightarrow C_2H_3\cdot$ (Melville, *Proc. Roy. Soc.*, in the press; activation energy 2·1 kcals.). If the activation energy of the reverse reaction is assumed to be *ca.* 3 kcals., the amended value for $Q_f(\cdot CHO, g.)$ becomes $-2{\cdot}6$ kcals. mole^{-1}.

$X_3C{-}CHO$ *Bond Dissociation Energies.*—We are now able to derive the C–C bond dissociation energies in chloral and bromal by substitution of the relevant Q_f values into equation (3). The results are summarised in Table III, together with other calculated dissociation energies obtained by use of the same Q_f values for the $-CX_3$ and $-CHO$ radicals.

TABLE III.

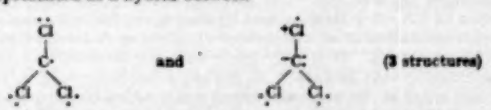
Bond dissociation energies.

	Q_f (kcals.).	$Q_f(CX_3)$.	Q_f (R).	$D(X_3C{-}R)$.
Cl_3CH	24	−15·4	−52·0	91·4
CCl_3	25·5	,,	−29·0	69·9
$Cl_3C{-}CHO$	44·0	,,	−2·6	62·0
$H_3C{-}CHO$	39·8	−32·1	,,	74·5
Br_3CH	−9 *	−48·4	−52·0	91·4 *
CBr_3	−18·5 *	,,	−26·7	56·6
$Br_3C{-}CHO$	11·4	,,	−2·6	62·4

* Assumed or estimated values (see text).

The similarity in the calculated $X_3C{-}CHO$ dissociation energies in chloral and bromal (the small difference of 0·4 kcal. between the values given in Table III is probably not real) should be linked with our assumption of equivalence in the values $D(Cl_3C{-}H)$ and $D(Br_3C{-}H)$. If these were not identical, a corresponding displacement would be found between $D(Cl_3C{-}CHO)$ and $D(Br_3C{-}CHO)$.

It may be noted that the C–C bond in chloral is some 12·5 kcals. weaker than C–C in acetaldehyde. This weakening may be compared with that between the C–Cl bonds in methyl chloride ($D = 80{\cdot}7$ kcals.) and carbon tetrachloride ($D = 69{\cdot}9$ kcals.), and also with the results of Davidson and Sullivan (*J. Chem. Physics*, **1949**, **17**, 776) who found that the C–Br bond in Cl_3CBr is at least 11 kcals. weaker than the C–Br bond in methyl bromide. The reason for the reduction in the strength of C–X bonds in $Cl_3C{-}X$ compared with $H_3C{-}X$ is probably (as suggested by Davidson and Sullivan) a resonance stabilization of the $\cdot CCl_3$ radical, the structure of which can be represented as a hybrid between



An alternative reason (that of steric repulsion between the relatively bulky Cl_3C group and X) encounters a difficulty in that the weakness of $Cl_3C{-}Br$ relative to $H_3C{-}Br$ is no more marked than the weakness of $Cl_3C{-}H$ relative to $H_3C{-}H$. In view of these facts it seems to us that the weakness of the C–C bond in chloral arises mainly from the resonance stabilization in the $\cdot CCl_3$ and $\cdot CHO$ radicals, and that steric repulsion effects are here probably small (of the order 1—2 kcals.).

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395. *Some Reactions of* p-*Tolyl Toluene*-p-*thiolsulphonate.*

By H. T. Hookway.

p-Tolyl toluene-*p*-thiolsulphonate has been shown to react with hydroxylamine in solutions of varying acidity to give toluene-*p*-sulphonamide and di-*p*-tolyl disulphide. The reaction of phenylhydrazine with the thiolsulphonic ester under similar experimental conditions yielded di-*p*-tolyl disulphide, toluene-*p*-sulphonylphenylhydrazide, and the phenylhydrazine salt of toluene-*p*-sulphinic acid.

Recently the author has drawn attention to the formation of *p*-tolyl toluene-*p*-thiolsulphonate by the interaction of carboxylic acid chlorides and salts of toluene-*p*-sulphinic acid (*J. Amer. Chem. Soc.*, 1949, **71**, 3240). Other workers (Kohler and Macdonald, *Amer. Chem. J.*, 1899, **22**, 219) by using similar experimental conditions had previously described the isolation of products which were thought to be α-keto-sulphones and which were stated to react with typical carbonyl-group reagents. It was therefore of interest to investigate the behaviour of *p*-tolyl toluene-*p*-thiolsulphonate towards reagents such as hydroxylamine and phenylhydrazine. Preliminary results (Hookway, *loc. cit.*) had shown that in buffered acetic acid solution both phenylhydrazine and hydroxylamine reacted with the thiolsulphonate to give, amongst other products, di-*p*-tolyl disulphide: the work reported in this paper is an extension of these experiments.

It is well known that thiolsulphonic esters are unstable in alkaline solution (see, *e.g.*, Zincke, *Annalen*, 1912, **391**, 55; 1914, **406**, 103), breaking down to give the salt of a sulphinic acid and a disulphide. It is possible that the formation of a sulphenic acid is an essential intermediate step in this decomposition (Child and Smiles, *J.*, 1924, 180):

$$RSO_2SR \longrightarrow RSO_2^- + RS^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$RS^+ + OH^- \longrightarrow RS{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$2RS{\cdot}OH \longrightarrow RSO_2H + RSH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$RS{\cdot}OH + RSH \longrightarrow RS{\cdot}SR + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The formation of thiolsulphonic esters by heating sulphinic acids with aqueous mineral acids may also be explained on the assumption that sulphenic acids are intermediate products (discussed by Kharasch *et al.*, *Chem. Reviews*, 1946, **39**, 269):

$$2RSO_2H \longrightarrow RS{\cdot}OH + RSO_3H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$RSO_2H + RS{\cdot}OH \longrightarrow RSO_2{\cdot}SR + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

When *p*-tolyl toluene-*p*-thiolsulphonate was heated in aqueous alcoholic solution with hydroxylamine hydrochloride and sodium acetate at an apparent pH of 5·5, the reaction products isolated were toluene-*p*-sulphonamide and di-*p*-tolyl disulphide. If the reaction shown in equation (6) above is reversible in acid solution, a probable mechanism for the formation of toluene-*p*-sulphonamide is:

$$C_7H_7{\cdot}SO_2{\cdot}S{\cdot}C_7H_7 + H_2O \rightleftharpoons C_7H_7{\cdot}S{\cdot}OH + C_7H_7{\cdot}SO_2H \quad . \quad . \quad . \quad . \quad (7)$$

$$C_7H_7{\cdot}SO_2H + NH_2{\cdot}OH \longrightarrow C_7H_7{\cdot}SO_2{\cdot}NH_2 + H_2O \quad . \quad . \quad . \quad . \quad (8)$$

The formation of di-*p*-tolyl disulphide can then be accounted for by reactions of the type summarised in equations (3) and (4). The disulphide could not have been produced by atmospheric oxidation of toluene-*p*-thiol formed by decomposition of toluene-*p*-sulphenic acid, since in an experiment conducted in an atmosphere of nitrogen di-*p*-tolyl disulphide was again obtained, but no toluene-*p*-thiol. It is very likely that the formation of toluene-*p*-sulphonamide involves the intermediate formation of toluene-*p*-sulphinic acid or of the toluene-*p*-sulphinyl anion in acid solution, for when xanthhydrol was added to a typical reaction mixture of thiolsulphonate and hydroxylamine hydrochloride in aqueous solution *p*-tolyl xanthyl sulphone was obtained. Xanthhydrol is known to give a carbonium cation very readily in acid solution and *p*-tolyl xanthyl sulphone was obtained independently by reaction between toluene-*p*-sulphinic acid and xanthhydrol in acetic acid solution (Thain, Thesis, London, 1949). Further, heating toluene-*p*-sulphinic acid in aqueous alcohol–acetic acid with hydroxylamine gave toluene-*p*-sulphonamide, but no di-*p*-tolyl disulphide could be isolated. Evaporation of an aqueous solution of toluene-*p*-sulphinic acid and excess of hydroxylamine is known to yield toluene-*p*-sulphonamide (Halssig, *J. pr. Chem.*, 1897, (2), **56**, 213).

It was found that lowering the pH of the thiolsulphonate reaction mixture resulted in a progressive decrease in the reaction velocity. This observation is in harmony with the view

now advanced, since decreasing pH may be expected to favour an equilibrium more and more to the left of equation (7).

When attention was directed to the reaction between *p*-tolyl toluene-*p*-thiolsulphonate and phenylhydrazine in aqueous alcohol–acetic acid, it was found that the products were di-*p*-tolyldisulphide, toluene-*p*-sulphonylphenylhydrazide, and phenylhydrazine toluene-*p*-sulphinate. Heating toluene-*p*-sulphinic acid with phenylhydrazine under the same reaction conditions gave principally the phenylhydrazine salt of the acid together with a very small amount of toluene-*p*-sulphonylphenylhydrazide. It is probable that the first step in the reaction between the thiolsulphonate and phenylhydrazine involves cleavage of the ester into toluene-*p*-sulphinyl anion and toluene-*p*-thio-cation. The toluene-*p*-sulphinyl fragment then forms the phenylhydrazine salt of toluene-*p*-sulphinic acid; the toluene-*p*-thio-ion forms toluene-*p*-sulphenic acid, this in turn disproportionating to give toluene-*p*-thiol and toluene-*p*-sulphinic acid [equation (3), R = C_7H_7]. In addition to these reactions, however, the toluene-*p*-thio-cation can abstract a hydrogen atom with its bonding electrons from phenylhydrazine to give toluene-*p*-thiol and a phenylhydrazine cation. Toluene-*p*-sulphinyl anions may then react with the positively-charged phenylhydrazine residue to give toluene-*p*-sulphonylphenylhydrazide, whilst the toluene-*p*-thiol reacts with toluene-*p*-sulphenic acid produced by the alternative reaction path to give di-*p*-tolyl disulphide. The very small yield of toluene-*p*-sulphonylphenylhydrazide obtained when toluene-*p*-sulphinic acid was heated with phenylhydrazine may be attributable to the fact that, unlike the reaction of this acid with hydroxylamine, the formation of the substituted phenylhydrazide requires the presence of toluene-*p*-thio-ions as well as toluene-*p*-sulphinic acid. Toluene-*p*-sulphinic acid slowly forms the corresponding thiolsulphonate in acetic acid solution; the yield of toluene-*p*-sulphonylphenylhydrazide obtained in the experiment described above corresponded approximately to that expected from the thiolsulphonate which would have been produced if the sulphinic acid had been heated alone with acetic acid.

Experimental.

p-*Tolyl Toluene*-p-*thiolsulphonate*.—This was prepared from toluene-*p*-sulphinic acid by Hilditch's method (*J.*, 1910, 1096), and had m. p. 78°.

Reactions of p-*Tolyl Toluene*-p-*thiolsulphonate with Hydroxylamine*.—All pH measurements were carried out on a "Cambridge" meter using a glass–silver/silver chloride electrode system. The pH values quoted are only intended to give a qualitative estimate of the "acidity" of the reaction mixtures.

(*a*) pH 5·5. Hydroxylamine hydrochloride (0·3 g., 0·0043 mol.) and sodium acetate (0·3 g., 0·0037 mol.) were dissolved in water (2 ml.) and added to a solution of *p*-tolyl toluene-*p*-thiolsulphonate (0·3 g., 0·0011 mol.) in ethyl alcohol (10 ml.; 96%). After 1½ hours at 70° the reaction mixture was cooled to room temperature. Needle-like crystals of di-*p*-tolyl disulphide (0·05 g.), m. p. 46—47° (crystallised from 96% alcohol), were deposited. Further working up of the reaction mixture gave toluene-*p*-sulphonamide (0·13 g.), m. p. 138·5—139° (white plates from water) (Found: C, 49·5; H, 5·5; N, 8·2. Calc. for $C_7H_9O_2NS$: C, 49·2; H, 5·3; N, 8·2%). The m. p. was not depressed on admixture with authentic sample of toluene-*p*-sulphonamide.

(*b*) pH 3. The thiolsulphonate (0·3 g.) was dissolved in a solution of hydroxylamine hydrochloride (0·4 g.) in aqueous alcohol (5 ml. of 96% alcohol + 2 ml. of water). After being heated at 70° for 2½ hours the reaction mixture yielded toluene-*p*-sulphonamide (0·06 g.)

(*c*) pH 1·5. The same quantities of reagents were used as in experiment (*b*), but concentrated hydrochloric acid (0·03 ml.) was added to bring the pH to 1·5. After being heated for 4 hours at 70°, thiolsulphonate (0·2 g.) was recovered and toluene-*p*-sulphonamide (0·03 g.) obtained.

(*d*) pH 7. Sodium hydroxide (1·4 ml.; 6N.) was added to a solution of hydroxylamine hydrochloride (0·4 g.) in aqueous alcohol (5 ml. of 96% alcohol + 2 ml. of water). Thiolsulphonate (0·3 g.) was then added and the mixture kept at 70° for 1½ hours. Di-*p*-tolyl disulphide (0·06 g.), m. p. 47—48°, and toluene-*p*-sulphonamide (0·16 g.), m. p. 138°, were obtained.

(*e*) *The reaction in nitrogen atmosphere*. Hydroxylamine hydrochloride (1·2 g.), sodium acetate (1·2 g.), and *p*-tolyl toluene-*p*-thiolsulphonate (1·0 g.) were dissolved in aqueous alcohol (20 ml. of 96% alcohol + 10 ml. of water). A slow stream of pure nitrogen was bubbled through the reaction vessel. The reaction mixture was kept at 70° for 6 hours and then stored overnight under nitrogen. Di-*p*-tolyl disulphide (0·25 g.) and toluene-*p*-sulphonamide (0·6 g.) were obtained.

The Reaction of p-*Tolyl Toluene*-*p*-*thiolsulphonate with Xanthhydrol*.—Hydroxylamine hydrochloride (0·6 g.) was dissolved in water (3 ml.) and added to a solution of the thiolsulphonate (0·5 g.) in alcohol (12 ml.; 96%). Xanthhydrol (0·3 g.) was then added and the solution kept at 70° for 5 hours. After 6 days at room temperature the crystals which had deposited (0·2 g.) were filtered off and crystallised from 96% alcohol. M. p. and mixed m. p. (with authentic specimen of *p*-tolyl xanthyl sulphone) 206—207°.

The Reaction between Toluene-p-*sulphinic Acid and Hydroxylamine*.—Toluene-*p*-sulphinic acid (0·7 g.) was dissolved in a solution of sodium acetate (1·2 g.) and hydroxylamine hydrochloride (1·2 g.) in water (7 ml.). After the solution had gently refluxed for 10 hours and then cooled to room temperature, crystals of toluene-*p*-sulphonamide (0·45 g.) were deposited.

The Reaction between Phenylhydrazine and p-*Tolyl Toluene*-p-*thiolsulphonate*.—Phenylhydrazine hydrochloride (1·5 g.) and sodium acetate (1·5 g.) were dissolved in water (10 ml.), and added to a solution

of the thiolsulphonate (1·0 g.) in alcohol (25 ml.; 96%). The reaction mixture was kept at 70° for 2 hours and then stored at room temperature for 3 days. The crystals of di-*p*-tolyl disulphide (0·27 g.) which had separated were filtered off; they had m. p. 46—47°. The aqueous-alcoholic mother-liquors were evaporated to dryness on the steam-bath, and the residue was extracted with hot water (25 ml.). The insoluble residue was filtered off from the hot solution and gave, after crystallisation from ethyl alcohol, toluene-*p*-sulphonylphenylhydrazide (0·15 g.), m. p. and mixed m. p. (with authentic specimen) 155° (rapid heating; decomp. at m. p.) (Found: C, 59·6; H, 5·4. Calc. for $C_{13}H_{14}O_4N_2S$: C, 59·5; H, 5·35%).

On cooling, the hot aqueous extract deposited crystals (0·45 g.), m. p. 155° (decomp.), which were shown to be phenylhydrazine toluene-*p*-sulphinate. This salt (0·45 g.) was dissolved in excess of cold sodium hydroxide solution (10 ml.; 1*N*.) and extracted twice with ether (2 × 10 ml.). The alkaline solution was acidified with dilute hydrochloric acid and toluene-*p*-sulphinic acid (0·2 g.), m. p. 83—84° (from ether–benzene), was precipitated. The ethereal extract yielded phenylhydrazine (acetyl derivative, m. p. 127°).

Note: Toluene-*p*-sulphonylphenylhydrazide was insoluble in cold dilute aqueous alkali.

Toluene-p-sulphonylphenylhydrazide.—Prepared by Troeger and Uhlmann's method (*J. pr. Chem.* 1895, (2), **51**, 442), this compound had m. p. 155° (decomp.).

The Reaction between Toluene-p-sulphinic Acid and Phenylhydrazine.—Toluene-*p*-sulphinic acid (0·7 g.) was added to a solution of phenylhydrazine hydrochloride (1·5 g.) and sodium acetate (1·5 g.) in aqueous alcohol (20 ml. of 96% alcohol + 5 ml. of water), and the mixture kept at 70° for 2 hours. On cooling, a bulky white precipitate (0·85 g.) was obtained, and evaporation of the mother-liquors to half the bulk yielded a further crop (0·25 g.) of crystals. The combined yields were extracted with hot water (45 ml.), the aqueous extract yielding phenylhydrazine toluene-*p*-sulphinate (1·08 g.), m. p. 155° (decomp.). The water-insoluble fraction gave toluene-*p*-sulphonylphenylhydrazide (0·01 g.), m. p. 155° (from 96% alcohol).

The Action of Glacial Acetic Acid on Toluene-p-sulphinic Acid.—(*a*) Toluene-*p*-sulphinic acid (1·0 g.) was dissolved in glacial acetic acid (10 ml.), and the solution gently refluxed for 2 hours. The mixture was poured into a large volume of saturated aqueous salt solution. The material which separated was *p*-tolyl toluene-*p*-thiolsulphonate (0·1 g.), m. p. 76° (from 96% alcohol) not depressed on mixture with an authentic specimen.

(*b*) The reaction time was increased to 10 hours. The yield of thiolsulphonate, m. p. 75—76°, was 0·45 g.

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396. *Inorganic Per-acids. Part II. The Alkali Percarbonates.*

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The contradictory experimental work on the alkali percarbonates has been re-investigated. The new compounds $CsOOH.H_2O_2$, $KHCO_4$, $RbHCO_4$, $Rb_2C_2O_6$, and $Li_2CO_4.H_2O$ were obtained. The compounds $NaHCO_4$, $Na_2C_2O_6$, $K_2C_2O_6$, $K_2CO_4.2\frac{1}{2}H_2O$, $K_2CO_4.H_2O_2.1\frac{1}{2}H_2O$, $K_2CO_4.2H_2O_2.H_2O$, $Rb_2CO_4.2\frac{1}{2}H_2O$, $Rb_2CO_4.H_2O_2.2H_2O$, $Rb_2CO_4.2H_2O_2.H_2O$, and $Cs_2CO_4.H_2O_2.H_2O$ were confirmed. The supposed isomeric compounds $Na_2CO_4.1\frac{1}{2}H_2O$ and $Na_2CO_4.H_2O_2.\frac{1}{2}H_2O$ were shown to be identical. The compounds $Na_2C_2O_6.H_2O_2$ and $Na_2C_2O_6.C_2H_5OH$ were not confirmed. The validity of the Riesenfeld test for differentiating between true percarbonates and carbonates with hydrogen peroxide of crystallisation is denied.

THE literature on the alkali percarbonates is very confused and contradictory, and it seems desirable first to give a short summary of the methods of preparation which have been used and then to consider briefly the supposed differentiation of the products into two groups, the true percarbonates regarded as salts of percarbonic acids, and the carbonate peroxyhydrates regarded as addition compounds of carbonates and hydrogen peroxide and sometimes water as well.

(1) Constam and Hansen (*Z. Elektrochem.*, 1896—1897, **3**, 137; Hansen, *ibid.*, p. 445) obtained sky-blue solid potassium perdicarbonate $K_2C_2O_6$ by anodic oxidation of concentrated potassium carbonate at −10°. They interpreted the reaction as due to the discharge of KCO_3' ions, but this is very improbable, since Löwenherz (*Z. physikal. Chem.*, 1895, **18**, 77) found that potassium carbonate is completely ionised in fused Glauber's salt into $2K^{\cdot}$ and CO_3''. Better yields and a purer product were obtained by Riesenfeld and Reinhold (*Ber.*, 1909, **42**, 4377), the poor yield found by Brown (*J. Amer. Chem. Soc.*, 1905, **27**, 1222) being no doubt due to faulty procedure. Constam and Hansen also obtained a solid thought to be rubidium perdicarbonate $Rb_2C_2O_6$ and oxidising solutions supposed to contain the sodium and ammonium salts. Solutions of the lithium and the sodium salt were obtained by Riesenfeld and Reinhold

and by LeBlanc and Zellmann (*Z. Elektrochem.*, 1923, **29**, 179, 192), who confirmed an observation of Salzer (*ibid.*, 1902, **8**, 900) that the yield is much better with normal sodium carbonate than with sodium hydrogen carbonate. Solutions which were merely assumed to contain percarbonates were obtained by Fichter and Bladergoen (*Helv. Chim. Acta*, 1927, **10**, 566) by the action of fluorine on solutions of sodium, potassium, and rubidium carbonates. It is seen that the only well-established electrolytic percarbonate is the potassium salt. This, and the oxidising solutions, liberate immediately iodine from neutral potassium iodide solution, and in the case of the potassium salt the iodine is equivalent to the whole of the active oxygen. The structure of the electrolytic perdicarbonates proposed by Constam and Hansen is $M_2[-O{\cdot}CO{\cdot}O{\cdot}O{\cdot}CO{\cdot}O-]$.

(2) Another type of percarbonate was isolated by Tanatar (*Ber.*, 1899, **32**, 1544). By dissolving sodium carbonate in 3% hydrogen peroxide and precipitating the products with alcohol he obtained two solids to which he gave the formulæ $Na_2CO_4.1\frac{1}{2}H_2O$ and $Na_2CO_4.\frac{1}{2}H_2O_2.H_2O$ (formed with excess of hydrogen peroxide). These liberated hydrogen peroxide in solution, slowly decomposing with evolution of oxygen, and gave hydrogen peroxide with acids. From thermochemical measurements, Tanatar concluded that the solids were, not carbonate peroxyhydrates, but salts of permonocarbonic acid H_2CO_4. Several patent specifications describe the preparation of sodium percarbonates by similar methods (Merck, G.P. 213,457/1907; Klopfer, G.P. 297,797/1914; Henkel & Cie., G.P. 303,556/1915; D. G. S. Scheideanst. Roessler, G.P. 342,046/1915; Wade, B.P. 152,366/1920; Noll, B.P. 202,985/1923; Shotterbeck, G.P. 560,460/1927; Walters, B.P. 565,653/1944; Slater and Wood, B.P. 568,754/1945). Tanatar failed to obtain the corresponding potassium salts in a pure form, the solid obtained being regarded as a mixture of $K_2CO_4.3H_2O$ and K_2CO_3. Kasanetzky (*J. Russ. Phys. Chem. Soc.*, 1902, **34**, 202, 388; *Abs.*, 1902, **82**, ii, 317, 500) by using 25% hydrogen peroxide obtained $K_2CO_4.2H_2O_2.\frac{1}{2}H_2O$ and $K_2CO_4.3H_2O_2$, which he regarded as $K_2CO_4.2\frac{1}{2}H_2O$ and $K_2CO_4.3H_2O$, an ammonium salt $(NH_4)_2CO_4.2H_2O$, and (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1110; *Abs.*, 1915, **108**, ii, 334) an unstable cæsium compound $Cs_2CO_4.2H_2O_2$. Peltner (*Ber.*, 1909, **42**, 1777) obtained the compound $RbOOH.H_2O_2$ and the unstable rubidium percarbonates $Rb_2CO_4.2\frac{1}{2}H_2O_2$, $Rb_2CO_4.H_2O_2.2H_2O$, and $Rb_2CO_4.2H_2O_2.H_2O$. By the action of excess of hydrogen peroxide on potassium and sodium hydrogen carbonates and precipitation with alcohol Kazanetzky (*J. Russ. Phys. Chem. Soc.*, 1903, **35**, 57; *Abs.*, 1913, **84**, ii, 366) obtained an evolution of carbon dioxide and the solid compounds $K_2CO_4.2\frac{1}{2}H_2O$, $Na_2CO_4.1\frac{1}{2}H_2O$, and $Na_2CO_4.\frac{1}{2}H_2O_2.H_2O$ (previously prepared by Tanatar from sodium carbonate). LeBlanc and Zellmann (*loc. cit.*) assumed that in this case sodium hydrogen carbonate forms the normal carbonate and carbonic acid in solution ($2NaHCO_3 = Na_2CO_3 + H_2CO_3$), the carbonate reacts with hydrogen peroxide to form Tanatar's salt, and the carbonic acid to form permonocarbonic acid which decomposes ($H_2CO_4 = H_2O + CO_2 + \frac{1}{2}O_2$). It would seem simpler, however, to suppose that the carbonic acid decomposes directly.

(3) A third group of reactions make use of the action of carbon dioxide on sodium peroxide hydrate $Na_2O_2.8H_2O$ (or sodium peroxide with less water than this), or sodium hydrogen peroxide NaOOH or its compound with hydrogen peroxide (Bauer, G.P. 145,746/1903; F.P. 331,937/1903; Merck, G.P. 188,569/1905; Wolffenstein and Peltner, *Ber.*, 1908, **41**, 280), or carbonyl chloride on sodium peroxide (Blankart, Dissert., Techn. Hochsch., Zurich, 1922). Wolffenstein and Peltner, by slowly passing carbon dioxide into a mixture of sodium peroxide and ice kept at or below 0°, and adding more sodium peroxide during the reaction, until the calculated increase in weight was reached, obtained $Na_2CO_4.1\frac{1}{2}H_2O$, the reaction being described as "subtle." By the further action of carbon dioxide on this, or directly by saturating hydrated sodium peroxide with carbon dioxide, they obtained $Na_2C_2O_6$, which they regarded as an anhydride of $NaHCO_3 + NaHCO_4$ but containing water, which they supposed was present as $Na_2CO_4.1\frac{1}{2}H_2O$. The action of carbon dioxide on sodium hydrogen peroxide NaOOH prepared by Tafel's method (*Ber.*, 1894, **27**, 2297) by the action of sodium peroxide on alcohol, which they regarded as "Natrylhydrat" $O{:}Na{\cdot}OH$, gave a product regarded as a mixture of $NaHCO_4$, Na_2CO_4, and $Na_2C_2O_6$, or of $NaHCO_4$, Na_2CO_4, and Na_2CO_3, or as $Na_4C_2O_7.H_2O$. Another specimen of sodium hydrogen peroxide prepared by the addition of sodium ethoxide to aqueous-alcoholic hydrogen peroxide was regarded as "Natriumtrioxyhydrat" $Na{\cdot}OOH$ and was supposed to give a different product with carbon dioxide, *viz.*, impure $NaHCO_4$ which was more stable to dehydration than that obtained with $O{:}Na{\cdot}OH$ and hence was regarded as isomeric with it. The supposed difference was almost certainly caused by a difference in the rates of drying of the two products, and there is no evidence that more than one form of NaOOH exists. They found that by the action of the calculated amount of carbon dioxide on partly

hydrated "O:Na·OH" hydrated Na_2CO_3 is formed. Dry sodium peroxide and sodium hydrogen peroxide do not react with dry carbon dioxide. Wolffenstein and Peltner emphasise that the amount of water present in their $Na_2C_2O_6$ does not allow the active oxygen to be present as hydrogen peroxide, and this must *a fortiori* apply to the nearly dry $K_2C_2O_6$ first described in the present communication.

Kamtikar and Husain (*J. Osmania Univ. Coll.*, 1934, **2**, 39; *Chem. Abstr.*, 1936, **30**, 4112) regarded $Na_2C_2O_6$ and $Na_2CO_4.1\frac{1}{2}H_2O$ prepared by the above methods as mixtures of Na_2CO_3, $NaHCO_3$, and a small amount of active oxygen probably in the form of Na_2O_2 or NaOOH. Both previous work in this field and the experiments now described negative this assumption. The preparations are far from simple. Wolffenstein and Peltner found that, in the preparation of Na_2CO_4 from carbon dioxide and hydrated sodium peroxide, if the water content is too small so much heat is evolved that the whole is decomposed, whilst with too much water the end product is moist and during the reaction the mass cakes together, the absorption of gas is too slow, and the percarbonate is decomposed. The reaction between carbon dioxide and sodium hydrogen peroxide they say is "tremendously sensitive"; the solid must be mixed with 26—30% of powdered ice, cooled in ice and salt, and the carbon dioxide passed in slowly. A local rise in temperature above 0° or a momentarily too rapid supply of carbon dioxide led to rapid and complete decomposition of the product. Even during drying of the moist product decomposition may occur, the lid of the desiccator being blown off, although when dry the solid is fairly stable. Failure to obtain satisfactory products in this field is very easy.

Riesenfeld and Mau (*Ber.*, 1911, **44**, 3589, 3595), on the basis of the Riesenfeld test (see below), concluded that $Na_2C_2O_6$ and Na_2CO_4 are true percarbonates, whilst $NaHCO_4$ is $Na_2C_2O_6.H_2O_2$ and $Na_2CO_4.H_2O$ is $Na_2CO_4.H_2O_2$, the compounds $Na_2C_2O_6$ and $Na_2C_2O_6.H_2O_2$ liberating the same amount of iodine from neutral potassium iodide solution. By passing dry carbon dioxide into sodium peroxide in absolute alcohol (containing NaOOH and $NaOC_2H_5$) at 0—5° until the mixture gave no colour with phenolphthalein they claimed to have obtained $Na_2C_2O_6.C_2H_5OH$, which is the same as Wolffenstein and Peltner's compound except that it contains alcohol of crystallisation, and if sodium peroxide hydrate was used $Na_2C_2O_6.\frac{1}{2}H_2O$ was obtained. By adding 30% hydrogen peroxide to the suspension of sodium peroxide in alcohol, either before or after passing in carbon dioxide, they claimed to have obtained $Na_2C_2O_6.H_2O_2$, and, whereas $Na_2C_2O_6$ liberated iodine equivalent to half the active oxygen, this liberated only a quarter. Kamtikar and Husain (*loc. cit.*) regarded the first compound as $Na_2CO_3.NaHCO_3.H_2O_2.xC_2H_5OH$, but we have shown that it is a mixture of $NaHCO_4$ and sodium monoethyl carbonate $NaO{\cdot}CO{\cdot}OC_2H_5$, obtained by Beilstein (*Annalen*, 1859, **112**, 124; Faurholt, *Z. physikal. Chem.*, 1927, **126**, 227) but apparently unknown to Riesenfeld and Mau. This compound is precipitated by carbon dioxide from sodium ethoxide solution and is insoluble in alcohol. Riesenfeld and Mau, using a potassium peroxide with the empirical formula K_2O_3 but probably a mixture of K_2O_4 and KO_2, in place of sodium peroxide, obtained a compound $K_2C_2O_6$ which, as solid or in solution, differed from the electrolytic compound in liberating only about half the iodine equivalent to its active oxygen. This compound was formulated as $M_2[-O{\cdot}O{\cdot}CO{\cdot}O{\cdot}CO{\cdot}O-]$. This type of isomerism is confirmed by experiments now described.

LeBlanc and Zellmann (*loc. cit.*) limited true percarbonates to salts of the monobasic permonocarbonic acid H_2CO_4 and the dibasic perdicarbonic acid $H_2C_2O_6$, which are derivatives of hydrogen peroxide HOOH in which one or both hydrogen atoms are replaced by the group O:C(OH), and they are hydrolysed by water as follows:

$$M_2C_2O_6 + H_2O = MHCO_4 + MHCO_3$$
$$MHCO_4 + H_2O = MHCO_3 + H_2O_2$$

The extensive liberation of iodine by $K_2C_2O_6$ was regarded as due to the rapid formation of $KHCO_4$ (then unknown as a solid, but described below). Wolffenstein and Peltner's compounds $Na_2C_2O_6$ and $NaHCO_4$ with 15% potassium iodide solution at −10° did not evolve oxygen, and only $NaHCO_4$ liberated iodine at once, whereas at 0° both liberated iodine immediately. The liberation of iodine by $Na_2C_2O_6$ at 0° was delayed by addition of sodium hydrogen carbonate, presumably owing to suppression of the formation of $NaHCO_4$. If both hydrogen atoms in HO·O·CO·OH are replaced by a metal the actve oxygen is no longer in the form of a true percarbonate but is easily detached as hydrogen peroxide of crystallisation. Although the extraction of hydrogen peroxide by ether from Tanatar's salt was only slight it was supposed (as we think incorrectly) that this was not $Na_2CO_4.1\frac{1}{2}H_2O$ but $Na_2CO_3.H_2O_2.\frac{1}{2}H_2O$. Wolffenstein and Peltner's Na_2CO_3 they regarded as a mixture of NaOOH and $NaHCO_4$.

It is clear from what precedes that the whole field of the chemistry of the alkali percarbonates stood in need of re-investigation. The following questions seemed to us to call for attention. (1) Is the salt $Na_2CO_4.1\frac{1}{2}H_2O$ described by Wolffenstein a chemical individual, and, if it is, does it differ from Tanatar's salt with the same formula? (2) Do the perdicarbonates $M_2C_2O_6$ exist in one form only, as stated by LeBlanc and Zellmann, or in two as stated by Riesenfeld and Mau? (3) Has the sodium percarbonate prepared from sodium peroxide and hydrogen peroxide in alcohol by the action of carbon dioxide the formula $Na_2C_2O_6.H_2O_2$ as stated by Riesenfeld and Mau, or is it a salt of H_2CO_4, and do other salts of this acid exist? (4) Is the test with neutral potassium iodide, claimed by Riesenfeld to distinguish true peroxides from hydrogen peroxide of crystallisation, reliable? Before passing to the experimental part, a few words may be said about the Riesenfeld test.

The distinction made by Riesenfeld and Reinhold and by Riesenfeld and Mau between the two types of compound is based on a reaction first studied by Bredig and Walton (*Z. Elektrochem.*, **1903**, **9**, 114; later investigations of it do not concern us), who found that hydrogen peroxide liberates hardly any iodine from neutral potassium iodide solution, but evolves oxygen gas. This was explained as a catalytic effect of the hypoiodite ion formed as an intermediate product:

$$H_2O_2 + I' = H_2O + IO' \text{ (slow)} \quad . \quad . \quad .

The marked hydrolysis of per-salts of weak acids such as boric, carbonic, and silicic makes it doubtful if the Riesenfeld test, when carried out with solutions, has any validity in such cases. It may be mentioned that the existence of free percarbonic acid in solution in ether (Bach, *Chem. Zentr.*, 1897, II, 828) was shown by Wolffenstein and Peltner (*loc. cit.*) to be improbable.

The results obtained in the present investigation were as follows.

Lithium permonocarbonate $Li_2CO_4.H_2O$ was prepared by the action of carbon dioxide on lithium peroxide perhydrate $Li_2O_2.H_2O_2.3H_2O$ or on lithium peroxide Li_2O_2 in presence of water; it is not formed by the action of hydrogen peroxide on lithium carbonate. Excess of carbon dioxide reduces the active oxygen without affecting the $Li_2O:CO_2$ ratio, which is explained by assuming the formation of unstable $Li_2C_2O_6$ or $LiHCO_4$, which could not be prepared.

The formation of disodium perdicarbonate $Na_2C_2O_6$ by the action of carbon dioxide on sodium peroxide hydrate was confirmed, but the compound described as $Na_2C_2O_6.C_2H_5{\cdot}OH$ was shown to be a mixture of sodium hydrogen permonocarbonate $NaHCO_4$ and sodium monoethyl carbonate $NaO{\cdot}CO{\cdot}OC_2H_5$. Sodium hydrogen permonocarbonate prepared from carbon dioxide and the compound $NaOOH.\frac{1}{2}H_2O_2$ was shown to lose carbon dioxide more readily than $Na_2C_2O_6$ and to form a product almost identical with Tanatar's salt; hence its formulation as $Na_2C_2O_6.H_2O_2$ is thought to be incorrect. Hydrogen peroxide has hardly any action on sodium hydrogen carbonate below 0°, but the evolution of carbon dioxide and the formation of $Na_2CO_4.\frac{1}{2}H_2O_2.H_2O$ at room temperature was confirmed. In presence of alcohol this absorbs carbon dioxide only if water is present, the active oxygen content being diminished. The distinction between $Na_2CO_4.1\frac{1}{2}H_2O$ and $Na_2CO_3.H_2O_2.\frac{1}{2}H_2O$ on the basis of Riesenfeld's test is shown to be unsatisfactory. When prepared from sodium peroxide octahydrate it behaves in the same way as Tanatar's salt, suggesting that in presence of sufficient water $Na_2C_2O_6$ and $Na_2O_2.8H_2O$ react to form a uniform substance, $Na_2CO_4.1\frac{1}{2}H_2O$ and $Na_2CO_3.H_2O_2.\frac{1}{2}H_2O$ being identical.

Potassium hydrogen permonocarbonate $KHCO_4$ was obtained by saturating an alcoholic suspension of potassium hydrogen peroxide with carbon dioxide at low temperature, and also from hydrogen peroxide and potassium monomethyl carbonate; it is much less stable than the sodium salt ($RbHCO_4$ is also unstable and $CsHCO_4$ could not be obtained). Hydrogen peroxide and sodium monomethyl or monoethyl carbonate or potassium monoethyl carbonate gave products containing active oxygen but probably partly hydrolysed. The formation of $K_2CO_4.2\frac{1}{2}H_2O$, $K_2CO_4.H_2O_2.1\frac{1}{2}H_2O$, and $K_2CO_4.2H_2O_2.H_2O$ from potassium carbonate and hydrogen peroxide in the ratios 1 : 1, 1 : 2, and 1 : 3 was confirmed. In alcohol all three absorbed carbon dioxide to form the same product $K_2C_2O_6$, which was obtained almost anhydrous by drying it in a vacuum over phosphoric oxide. Evidence for the formation of a small amount of $KHCO_4$ with excess of hydrogen peroxide was found.

Rubidium hydrogen permonocarbonate $RbHCO_4$ was confirmed; it is very unstable and sensitive to dehydration. With excess of hydrogen peroxide evidence of the formation of a substance containing more active oxygen was found but it could not be isolated. The three compounds $Rb_2CO_4.2\frac{1}{2}H_2O$, $Rb_2CO_4.2H_2O_2.H_2O$, and $Rb_2CO_4.H_2O_2.2H_2O$ were confirmed. In alcohol they absorb carbon dioxide in the same way as the potassium salts. With the first, absorption of carbon dioxide occurs with slight loss of active oxygen to form $Rb_2C_2O_6$ but this salt could not be obtained anhydrous. The active oxygen retained after carbonation of the second and third is greater than in the case of the potassium salts, and rubidium hydrogen permonocarbonate $RbHCO_4$ seems to be formed in appreciable amounts.

Cæsium hydrogen peroxide perhydrate $CsOOH.H_2O_2$ was prepared by the action of hydrogen peroxide on alcoholic cæsium hydroxide; with carbon dioxide it does not form $CsHCO_4$ but gives $Cs_2CO_4.H_2O_2.H_2O$.

Experimental.

1. *Lithium Permonocarbonate* $Li_2CO_4.H_2O$.—This compound, previously unknown, could not be obtained by the action of hydrogen peroxide on lithium carbonate, on account of the sparing solubility of the latter, but was prepared by the action of carbon dioxide on lithium peroxide perhydrate and on lithium peroxide in presence of water. In the analyses of the products, lithium oxide Li_2O was determined by titration with acid using methyl-orange as indicator, active oxygen (O_2) by titration with permanganate in acid solution, carbon dioxide gravimetrically by liberation and absorption in alkali, and water by difference.

1. *Action of hydrogen peroxide on lithium carbonate.* On keeping lithium carbonate in contact with 30% hydrogen peroxide for some time and filtering, it was found that the solid did not contain active oxygen but was unchanged lithium carbonate. The same result was found by using excess of hydrogen peroxide and keeping the mixture for a long time at room temperature or below 0°. From the mother-liquor, alcohol precipitated only lithium carbonate.

2. *Action of carbon dioxide on lithium peroxide perhydrate.* The preparation of lithium peroxide perhydrate ($Li_2O_2.H_2O_2.3H_2O$) was carried out as described by De Forcrand (*Compt. rend.*, 1900, **130**, 1465). Cold alcohol was added to a cold concentrated aqueous solution of lithium hydroxide containing the requisite amount of hydrogen peroxide. The compound separated as minute colourless crystals, which were washed with alcohol and ether after separation from the mother-liquor. On passage of a stream of carbon dioxide dried by concentrated sulphuric acid slowly over this substance with continuous stirring, the mass being maintained below −10°, the carbon dioxide was smoothly absorbed and towards the end of the reaction the already dry mass became moist. The end of the reaction is indicated when the increase in weight corresponds to the absorption of one molecule of carbon dioxide per mol. of Li_2O. The pasty mass was washed with alcohol and the crystalline white solid analysed after being washed with ether (analysis 1, Table I) and after drying for several hours in a vacuum over phosphoric oxide (analysis 2). The results show that a lithium percarbonate was formed. The product dried in a vacuum corresponds to $Li_2CO_4.H_2O$. Only half the active oxygen in the lithium peroxide perhydrate is found in the solid percarbonate, the rest being eliminated as hydrogen peroxide and removed during the washing. This salt is soluble in water to give an alkaline solution. Dry ether does not extract any active oxygen from it. On addition of the solid to concentrated neutral potassium iodide solution a slight liberation of iodine occurred, accompanied by a strong evolution of oxygen, which according to Riesenfeld and Reinhold would indicate that the product is an addition product of hydrogen peroxide and lithium carbonate. Since, however, it is not formed from hydrogen peroxide and lithium carbonate, it seems to be a true percarbonate, and the evolution of oxygen may owe its origin to free hydrogen peroxide formed by hydrolysis and to the alkaline reaction (hypoiodite is formed which reacts with hydrogen peroxide, evolving oxygen). The experiment was repeated but at the end of the reaction excess of 30% hydrogen peroxide was added. No increase in active oxygen content was found (analysis 3, directly after washing with alcohol and ether; analysis 4, after drying in a vacuum over phosphoric oxide for several hours). The salt has, therefore, no tendency to add hydrogen peroxide. The solid gradually lost active oxygen, and after a week the active oxygen content fell to 11·0%. The aqueous solution is very unstable, losing the whole of its active oxygen within a few hours. The active oxygen content is also affected by continued passage of carbon dioxide after one molecule of carbon dioxide is absorbed per mol. of Li_2O. In this way products were obtained with less active oxygen but at the same time no further increase in the ratio $CO_2 : Li_2O$ was observed. Analysis 5 corresponds to a product obtained after passing carbon dioxide for an hour after one molecule of carbon dioxide had been absorbed per mol. of Li_2O. This behaviour is best explained by assuming the formation of an unstable compound $Li_2C_2O_6$ or $LiHCO_4$, which decomposes as soon as formed:

$$2Li_2C_2O_6 = 2Li_2CO_3 + O_2 + 2CO_2$$
$$2LiHCO_4 = Li_2CO_3 + CO_2 + H_2O_2 + \tfrac{1}{2}O_2$$

A similar behaviour was noticed by Wolffenstein and Peltner in the preparation of barium percarbonate, and is in harmony with the fact that lithium hydrogen carbonate, like the alkaline-earth hydrogen carbonates, is unstable, in contrast to other alkali-metal hydrogen carbonates.

3. *Preparation from lithium peroxide* (Li_2O_2). Li_2O_2 was obtained by "dehydrating" $Li_2O_2.H_2O_2.3H_2O$ over phosphoric oxide in a vacuum, as described by De Forcrand. The preparation of lithium percarbonate from this peroxide was carried out in the same way as before; to obtain a good yield, the appropriate amount of water must be present. Analysis 6 was found when $Li_2O_2 : H_2O$ was 1 : 2, analysis (7) when the ratio was 1 : 3, and (8) when it was 1 : 5. The results show that the same percarbonate is formed, in good yield, when three molecules of water are present per Li_2O_2. The reaction therefore proceeds as follows:

$$Li_2O_2\,aq. + CO_2 = Li_2CO_4\,aq.$$

The product obtained in this way is identical in properties with that prepared from lithium peroxide perhydrate.

TABLE I.

Analysis no.	Li_2O, %.	CO_2, %.	O_2, %.	H_2O, %.	Li_2O.	CO_2.	O_2.	H_2O.
1	25·1	36·8	13·2	24·9	1	0·99	0·98	1·65
2	27·4	40·1	14·4	18·05	1	1·00	0·98	1·09
3	24·8	36·4	13·2	25·6	1	1·00	0·99	1·71
4	27·8	40·7	14·45	17·0	1	0·99	0·97	1·01
5	25·2	37·6	11·9	—	1	1·01	0·88	—
6	29·6	43·1	12·5	14·8	1	0·99	0·79	0·83
7	28·4	41·4	13·5	16·7	1	0·99	0·89	0·98
8	29·4	43·0	12·2	15·4	1	0·99	0·76	0·87
			Calc. for $Li_2CO_4.H_2O$:		1	1	1	1

II. *Sodium Percarbonates.*—In the following experiments, the determinations of Na_2O, CO_2, O_2, and H_2O were carried out as described above unless otherwise stated. The solids formed in the reactions were washed with alcohol and ether and dried on porous plates in a vacuum over the drying agents specified unless otherwise stated. Since some of the compounds are very sensitive to small changes in drying procedure, these details are given when required.

1. *Disodium perdicarbonate* $Na_2C_2O_6$. In the preparation Wolffenstein and Peltner's procedure was closely followed, carbon dioxide being passed slowly into hydrated sodium peroxide and the temperature kept below 0° until the weight no longer increased. The product was dried over phosphoric oxide for a day. (The moist product rapidly loses carbon dioxide and oxygen.) Analyses 1 and 2 in Table II refer to this compound. The results confirm those of Wolffenstein and Peltner and the amount

of water is too small for the active oxygen to exist as hydrogen peroxide, or the carbon dioxide as $NaHCO_3$. Dry ether had no effect on the active oxygen content. The solid liberated iodine and oxygen from concentrated neutral potassium iodide solution. Analyses **3** and **4** refer to solid kept for a month in a desiccator; loss of active oxygen and some carbon dioxide occurred but to a much smaller extent than with $NaHCO_4$ (see below), and the solid still liberated much iodine from iodide solution. The rapid loss of carbon dioxide from the moist product suggests the formation of $NaHCO_4$ by hydrolysis according to the scheme of LeBlanc and Zellmann.

TABLE II.

Analysis no.	Na_2O, %.	CO_2, %.	O_a, %.	H_2O, %.	Na_2O.	CO_2.	O_a.	H_2O.
1	38·8	49·0	7·7	4·4	1	1·78	0·77	0·39
2	38·9	48·9	7·8	4·3	1	1·76	0·78	0·38
3	41·8	48·2	5·8	4·2	1	1·62	0·54	0·35
4	41·5	48·45	5·7	4·4	1	1·64	0·53	0·36
				Calc. for $Na_2C_2O_4$:	1	2	1	

Riesenfeld and Mau's method was also used, dry sodium peroxide in absolute alcohol being saturated with dry carbon dioxide below 0° until phenolphthalein gave no colour. The product was dried for a short time. Na_2O and CO_2 were determined by titration with methyl-orange and phenolphthalein. The results are shown in Table III.

TABLE III.

Analysis no.	Na_2O, %.	CO_2, %.	O_a, %.	Na_2O.	CO_2.	O_a.
1	29·2	37·4	4·8	1	1·81	0·64
2	29·5	38·25	5·2	1	1·83	0·69

This product when distilled with water gave alcohol even after repeated washing with ether and when kept lost carbon dioxide much more rapidly than that prepared by the first method. Its properties suggest that it is a mixture of the unstable $NaHCO_4$ and sodium monoethyl carbonate $NaO{\cdot}CO{\cdot}O{\cdot}C_2H_5$, and not $Na_2C_2O_4.C_2H_5{\cdot}OH$ as stated by Riesenfeld and Mau. It is probable that sodium peroxide first reacts with alcohol as follows:

$$Na_2O_2 + C_2H_5{\cdot}OH = NaOOH + NaO{\cdot}C_2H_5$$

and the two products react simultaneously with carbon dioxide:

$$NaOOH + CO_2 = NaHCO_4$$
$$NaOC_2H_5 + CO_2 = NaO{\cdot}CO{\cdot}O{\cdot}C_2H_5$$

An equimolecular mixture of these products would have the same composition as $Na_2C_2O_6.C_2H_5{\cdot}OH$. This mechanism is confirmed by the experiment described in (2).

2. *Sodium hydrogen monopercarbonate* $NaHCO_4$. The method of LeBlanc and Zellmann was used, except that $NaOOH,\frac{1}{2}H_2O_2$ prepared according to Wolffenstein and Peltner was used instead of NaOOH. A mixture of 30% hydrogen peroxide and alcohol was added to alcoholic sodium ethoxide (H_2O_2 : Na = 2 : 1). The oily precipitate solidified on cooling. The solid washed with alcohol and ether gave Na_2O 41·9, 41·8%, O_a 29·9, 29·8%, *i.e.*, Na : O_a 1 : 1·39 and 1 : 1·38; $NaOOH,\frac{1}{2}H_2O_2$ requires 1 : 5. The solid (2 g.) was suspended in 75% alcohol (100 ml.), and carbon dioxide passed in below −10° until phenolphthalein gave no colour. The product was dried over phosphoric oxide for a short time. The results 1 and 2 in Table IV show that the solid is $NaHCO_4$. The product was free from alcohol, was not affected by dry ether, and liberated iodine and oxygen from potassium iodide solution. Rapid drying caused sudden decomposition, but this did not occur on slow drying. The results **3** and **4** for a specimen kept for a month show that carbon dioxide and active oxygen are lost more rapidly than from $Na_2C_2O_4$; the final product behaves like Tanatar's salt:

$$2NaHCO_4 = Na_2CO_4 + H_2O + CO_2 + \tfrac{1}{2}O_2.$$

TABLE IV.

Analysis no.	Na_2O, %.	CO_2, %.	O_a, %.	H_2O, %.	Na.	CO_2.	O_a.	H_2O.
1	31·3	41·6	14·9	12·15	1	0·94	0·92	0·67
2	31·2	40·6	14·8	13·4	1	0·92	0·91	0·74
3	41·0	34·6	11·7	12·6	1	0·59	0·55	0·53
4	41·4	35·1	11·5	12·1	1	0·59	0·54	0·50
5	30·5	41·1	14·3	14·1	1	0·95	0·91	0·79
6	30·2	40·2	14·3	15·4	1	0·94	0·92	0·87
7	23·9	29·6	11·1	*	1	0·88	0·90	*
8	23·3	28·6	11·0	*	1	0·87	0·92	*
				Calc. for $NaHCO_4$:	1	1	1	0·50

* Contains alcohol.

The procedure of Riesenfeld and Mau, said to give $Na_2C_2O_6.H_2O_2$, was then followed. 30% Hydrogen peroxide was added to alcoholic sodium peroxide before saturating the mixture with carbon dioxide. The product was easily freed from alcohol by washing with ether, and analyses **5** and **6** show that it was $NaHCO_4$: $C_2H_5ONa + H_2O_2 = NaOOH + C_2H_5OH$; $NaOOH + CO_2 = NaHCO_4$. When 30%

hydrogen peroxide was added after the reaction with carbon dioxide a slimy product was formed, not easily freed from alcohol by washing with ether and resembling the product containing active oxygen formed by addition of hydrogen peroxide to sodium monoethyl carbonate suspended in alcohol. In this reaction the carbon dioxide forms sodium monoethyl carbonate with the sodium peroxide and alcohol, and the hydrogen peroxide added subsequently reacts with this to give the slimy product which contaminates the $NaHCO_4$. Contrary to Riesenfeld and Mau's statement, the results are quite different according as hydrogen peroxide is added before or after passage of carbon dioxide, and confirm the conclusion that the compound described by them as $Na_2C_2O_6.H_2O_2$ is really a mixture of $NaHCO_4$ and sodium monoethyl carbonate.

3. *Action of hydrogen peroxide on sodium hydrogen carbonate.* The gradual addition of excess of solid sodium hydrogen carbonate to 10% or 30% hydrogen peroxide at room temperature or below 0° gave a solid free from active oxygen. But if the solid was set aside at room temperature in contact with the solution for about 4 hours Tanatar's salt $Na_2CO_4.\frac{1}{2}H_2O_2.H_2O$ was formed, provided that sufficient hydrogen peroxide was used. The change was very slow below 0°. On passage of carbon dioxide into an alcoholic suspension of Tanatar's salt, no $NaHCO_4$ or $Na_2C_2O_6$ was formed, the gas being absorbed only in presence of water, and active oxygen being lost simultaneously.

4. *Disodium permonocarbonate* $Na_2CO_4.1\frac{1}{2}H_2O$. This was prepared by Wolffenstein and Peltner's method. Carbon dioxide was passed slowly into 7·8 g. of sodium peroxide and 5 g. of water cooled below 0° until the increase in weight corresponded with the formation of Na_2CO_4. The washed product was dried in a vacuum for a short time. The analytical results were :

Analysis no.	Na_2O, %.	CO_2, %.	O_a, %.	H_2O, %.	Na_2O.	CO_2.	O_a.	H_2O.
1	40·7	29·2	9·5	20·7	1	1·01	0·90	1·75
2	40·8	30·0	9·4	19·8	1	1·04	0·89	1·67

The product was unstable and differed in this respect from Tanatar's salt, but was more stable when not fully dried. It liberated iodine and oxygen from concentrated neutral potassium iodide solution. The product from $Na_2O_2.8H_2O$ behaved like Tanatar's salt in not liberating iodine, and it is concluded that the action of carbon dioxide on sodium peroxide hydrate containing less than $8H_2O$ gives Tanatar's salt, $Na_2C_2O_6$ (liberating iodine), and unchanged sodium peroxide hydrate. But, with sufficient water, $Na_2C_2O_6$ and sodium peroxide hydrate react to form Tanatar's salt. Riesenfeld and Mau's supposition that the product is a definite percarbonate different from Tanatar's salt, on the basis of a slight liberation of iodine, is considered very unlikely.

III. *Potassium Percarbonates.*—1. *Action of hydrogen peroxide on potassium carbonate.* Potassium carbonate was dissolved in 30% hydrogen peroxide in different proportions below −5° and excess of alcohol added. The oily products solidified on cooling; they were washed as usual and dried for a short time over calcium chloride in a vacuum. The white crystalline solids were readily soluble, the solutions decomposing rapidly. When the solids were added to concentrated neutral potassium iodide solution oxygen was evolved but no iodine liberated. The solids slowly decomposed but no yellow colour developed (as with $KHCO_4$, see below). The analyses are given in Table V.

TABLE V.

Ratio $K_2CO_3 : H_2O_2$.	K_2O, %.	CO_2, %.	O_a, %.	H_2O, %.	K_2O.	CO_2.	O_a.	H_2O.
(*a*) 1 : 1	46·5	21·7	7·7	24·2	1	0·99	0·97	2·71
	46·7	21·7	7·8	23·7	1	1·00	0·98	2·65
			Calc. for $K_2CO_4.2\frac{1}{2}H_2O$:		1	1	1	2·5
(*b*) 1 : 2	43·4	20·25	14·3	22·05	1	1·00	1·94	2·65
	43·45	20·3	14·4	21·8	1	1·00	1·94	2·62
			Calc. for $K_2CO_4.H_2O_2.1\frac{1}{2}H_2O$:		1	1	2	2·5
(*c*) 1 : 3	38·65	18·2	18·8	24·4	1	1·01	2·85	3·29
	39·0	18·1	19·0	23·9	1	0·99	2·87	3·19
(*d*) 1 : 5	38·7	18·0	18·9	24·4	1	0·99	2·86	3·28
			Calc. for $K_2CO_4.2H_2O_2.H_2O$:		1	1	3	3

2. *Effect of carbon dioxide on the above products.* Carbon dioxide when passed into alcoholic suspensions of the above products was absorbed and the same substance was formed in all cases. The temperature was kept below −10° until phenolphthalein gave no colour. In case (*a*) practically all the active oxygen was retained, in (*b*) only half, and in (*c*) only a third. The products in all cases contained $K_2C_2O_6$ and water. They were unstable, losing nearly half the active oxygen in a week. They were unchanged by dry ether but easily soluble in water to form unstable solutions. The solids liberated considerable quantities of iodine from concentrated neutral potassium iodide solution. Drying over phosphoric oxide in a vacuum for a few hours caused loss of water and some active oxygen. The analytical results exclude the possibility that the products (*a*)—(*d*) consist of potassium hydrogen carbonate with hydrogen peroxide of crystallisation and since they all form $K_2C_2O_6$, which can be obtained nearly anhydrous, by the action of carbon dioxide they are probably as formulated, and not $K_2CO_3.H_2O_2.1\frac{1}{2}H_2O$, $K_2CO_3.2H_2O_2.\frac{1}{2}H_2O$, and $K_2CO_3.3H_2O_2$. The absorption of carbon dioxide by them would then proceed as follows ($x = 0$, 1, or 2) :

$$K_2CO_4.xH_2O_2\,aq. + CO_2 = K_2C_2O_6\,aq. + xH_2O_2$$

The analyses of the products from (*a*)—(*c*) are given in Table VI, the effects of drying being shown in the last two lines.

TABLE VI.

Initial substance.	K_2O, %.	CO_2, %.	O_2, %.	H_2O_2, %.	K_2O.	CO_2.	O_2.	H_2O_2.
(*a*)	43·2	38·8	6·8	11·2	1	1·92	0·93	1·35
	44·2	39·2	7·05	9·5	1	1·90	0·94	1·13
(*b*)	43·0	39·0	7·2	10·8	1	1·93	0·98	1·31
	43·8	39·4	7·1	9·65	1	1·92	0·96	1·15
(*c*)	43·7	39·1	7·3	9·9	1	1·91	0·99	1·18
	43·0	38·3	7·2	11·4	1	1·91	0·99	1·38
(*a*)	47·9	42·85	6·8	2·4	1	1·91	0·84	0·26
(*b*)	47·8	43·0	6·9	2·3	1	1·92	0·85	0·25
				Calc. for $K_2C_2O_4$:	1	2	1	

3. *Potassium hydrogen permonocarbonate* $KHCO_4$. (i) Although LeBlanc and Zellmann pointed out the possibility of the formation of this compound in the hydrolysis of $K_2C_2O_4$ it was not isolated. We obtained *potassium hydrogen permonocarbonate* $KHCO_4$ by the action of carbon dioxide on an alcoholic suspension of potassium hydrogen peroxide perhydrate, $KOOH,\frac{1}{2}H_2O_2$, made according to D'Ans and Friederich (*Z. anorg. Chem.*, 1912, **73**, 326). A mixture of 30% hydrogen peroxide and alcohol was added to a solution of potassium ethoxide in absolute alcohol cooled below $-10°$ ($K : H_2O_2 = 1 : 1$). The oily product solidified after cooling for some time. Carbon dioxide was passed into the alcoholic suspension, the temperature being kept below $-10°$. When phenolphthalein was no longer coloured the fine crystalline precipitate was filtered off rapidly, washed with cold ether, and analysed as rapidly as possible. Results 1 and 2 in Table VII are for two specimens. The solid is very unstable unless kept below 0°. It liberates much iodine as well as oxygen from concentrated neutral potassium iodide solution. On drying it decomposes rapidly, becoming pinkish-yellow and leaving potassium hydrogen carbonate. The colour may be due to $K_2C_2O_6$, but this was not isolated

(ii) A similar product was obtained by the action of 30% hydrogen peroxide on potassium monomethyl carbonate $CH_3O{\cdot}CO{\cdot}OK$ in methyl alcohol. This was precipitated on passing dry carbon dioxide into a solution of potassium methoxide in methyl alcohol. When phenolphthalein gave no colour, 30% hydrogen peroxide was added ($K : H_2O_2 = 1 : 2$) with stirring, the temperature being kept below $-10°$. The product was washed thoroughly with dry ether and was free from methyl alcohol. The analyses are 3 and 4 in Table VII. Unless anhydrous methyl alcohol was used, partial hydrolysis of potassium monomethyl carbonate occurred and the product formed with hydrogen peroxide was deficient in active oxygen.

(iii) Some evidence for the formation of very small amounts of $KHCO_4$ from $K_2C_2O_4$ and excess of hydrogen peroxide by the reaction $K_2C_2O_4 + H_2O_2 = 2KHCO_4$ was obtained. Carbon dioxide was passed to saturation into an alcoholic suspension of $K_2CO_4,2H_2O_2,H_2O$ in presence of excess of 30% hydrogen peroxide ($K : H_2O_2 = 1 : 4$) and the washed product gave the analyses 5 and 6 in Table VII. The active oxygen content is more than that required for $K_2C_2O_4$. The product was sensitive to dehydration and developed a slight yellow colour, observed with $KHCO_4$.

TABLE VII.

Analysis no.	K_2O, %.	CO_2, %.	O_2, %.	H_2O_2, %.	K.	CO_2.	O_2.	H_2O_2.
1	38·95	33·9	12·1	15·1	1	0·93	0·91	1·01
2	39·9	33·7	12·5	13·9	1	0·90	0·92	0·91
3	40·2	34·5	12·2	13·0	1	0·92	0·89	0·85
4	39·85	34·7	12·4	13·1	1	0·93	0·91	0·83
5	41·8	37·8	8·0	12·4	1	0·96	0·56	0·78
6	42·6	38·3	8·3	10·9	1	0·96	0·57	0·67
				$KHCO_4$ requires	1	1	1	0·5

IV. *Rubidium Percarbonates.*—1. *Action of hydrogen peroxide on rubidium carbonate.* The method of Peltner was closely followed and his results confirmed. Rubidium carbonate was dissolved in 30% hydrogen peroxide, the liquid being cooled below $-5°$, and excess of absolute alcohol added. The oily product solidified on cooling and the white crystalline solids were washed as usual and dried for some time over calcium chloride. Rubidium was determined as sulphate. The properties of the products were similar to those of the corresponding potassium salts. Analyses are in Table VIII.

TABLE VIII.

Ratio $Rb_2CO_3 : H_2O_2$.	K_2O, %.	CO_2, %.	O_2, %.	H_2O_2, %.	Rb_2O.	CO_2.	O_2.	H_2O_2.
(*a*) 1 : 1	63·65	15·3	5·3	15·75	1	1·02	0·98	2·56
	62·9	14·9	5·3	16·0	1	0·99	0·97	2·61
				Calc. for $Rb_2CO_4,2\frac{1}{2}H_2O$:	1	1	1	2·5
(*b*) 1 : 2	58·2	13·6	9·5	18·7	1	0·99	1·91	3·37
	58·4	13·7	9·7	18·2	1	1·00	1·93	3·23
				Calc. for $Rb_2CO_4,H_2O_2,2H_2O$:	1	1	2	3
(*c*) 1 : 3	57·0	13·4	13·5	16·1	1	1·01	2·76	2·93
	56·4	13·2	13·2	17·2	1	1·00	2·74	3·13
				Calc. for $Rb_2CO_4,2H_2O_2,H_2O$:	1	1	3	3

2. *Preparation of* $Rb_4C_4O_9$. An alcoholic suspension of compound (*a*) in Table VIII was saturated below −10° with carbon dioxide. The white crystalline product was rapidly washed and analysed. Results 1 and 2 in Table IX indicate an absorption of almost one mole of CO_2 per mole of Rb_2CO_3 with slight loss of active oxygen, and formation of *rubidium perdicarbonate* $Rb_4C_4O_9$. This was much less stable than $K_4C_4O_9$ and on dehydration over phosphoric oxide lost all its active oxygen in a few hours without development of a yellow colour. It liberated a considerable amount of iodine and also oxygen from neutral concentrated potassium iodide solution.

3. *Formation of* $RbHCO_4$. An alcoholic suspension of compound (*b*) in Table VIII was treated as under (2). The results 3 and 4 in Table IX show an absorption of nearly one mole of CO_2 per mole of Rb_2CO_3 and an active oxygen content of more than one atom. The product was less sensitive to dehydration than $Rb_4C_4O_9$ but was affected and developed a yellow colour which suggests the presence of *rubidium hydrogen permonocarbonate* $RbHCO_4$. The latter was obtained in good yield by saturating an alcoholic suspension of (*c*) in Table VIII with carbon dioxide, the analyses being 5 and 6 in Table IX. It was also prepared from RbOOH obtained by the method of Peltner (*Ber.*, 1909, **42**, 1777) by adding 30% hydrogen peroxide mixed with absolute alcohol to an absolute-alcoholic solution of rubidium hydroxide ($Rb : H_2O_2 = 1 : 1$) cooled below −10°, the precipitated oil solidifying on cooling. The alcoholic suspension was saturated with carbon dioxide. The analyses of the washed product, made rapidly, are 7 and 8 in Table IX. The solid liberated much iodine and also oxygen from neutral concentrated potassium iodide solution; it was unstable on dehydration, leaving potassium hydrogen carbonate.

4. *Rubidium percarbonate with higher active oxygen content.* In the preparation of $RbHCO_4$ from RbOOH with the ratio $Rb : H_2O_2 = 1 : 2$ the product contained somewhat more active oxygen, as shown in analyses 9 and 10 in Table IX. A similar increase was found on saturating with carbon dioxide an alcoholic suspension of $Rb_2CO_4.2H_2O_2.H_2O$ in excess of hydrogen peroxide, and another percarbonate seems to be formed (but not in a pure state), which like $RbHCO_4$ and $Rb_4C_4O_9$ contains $2CO_2$ per Rb_2O but more active oxygen.

TABLE IX.

Analysis no.	Rb_2O, %.	CO_2, %.	O_2, %.	Rb_2O.	CO_2.	O_2.
(*a*) 1	59·6	26·9	4·5	1	1·92	0·89
2	59·0	26·4	4·5	1	1·90	0·90
			$Rb_4C_4O_9$ requires	1	2	1
(*b*) 3	57·2	25·85	7·6	1	1·92	1·56
4	56·4	25·2	7·8	1	1·90	1·61
(*c*) 5	54·6	24·1	8·3	1	1·88	1·78
6	57·6	25·7	8·9	1	1·90	1·80
(*d*) 7	56·9	24·9	8·8	1	1·86	1·80
8	56·7	24·55	8·7	1	1·84	1·78
			$RbHCO_4$ requires	1	2	
(*e*) 9	52·4	22·7	10·9	1	1·84	2·42
10	53·4	23·4	11·6	1	1·85	2·53

V. *Cæsium Percarbonate.*—On addition of 30% hydrogen peroxide mixed with alcohol to a solution of cæsium hydroxide in absolute alcohol ($Cs : H_2O_2 = 1 : 1$) an oil was formed which slowly solidified. After the salt had been washed with alcohol and ether the cæsium was determined as sulphate and the active oxygen by permanganate titration. The results correspond with *cæsium hydrogen peroxide perhydrate* $CsOOH,H_2O_2$: Cs, 59·5, 60·2; O_2, 12·9, 13·5; $Cs : O_2$, 1 : 1·80, 1 : 1·86; $CsOOH,H_2O_2$ requires 1 : 2.

On saturation of an alcoholic suspension of this compound with carbon dioxide at −10° the solid dissolved. Ether precipitated a white crystalline solid which did not liberate iodine from concentrated neutral potassium iodide solution but only oxygen. It slowly decomposed without formation of a yellow colour. The following analyses show that the compound was not $CsHCO_4$ as expected, but cæsium permonocarbonate peroxide hydrate $Cs_2CO_4.H_2O_2.H_2O$, described by Kasanetzky.

Cs_2O, %.	CO_2, %.	O_2, %.	Cs_2O.	CO_2.	O_2.
68·2	10·7	7·5	1	1·00	1·94
67·7	10·5	7·3	1	1·00	1·91
	Calc. for $Cs_2CO_4.H_2O_2.H_2O$:		1	1	2

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397. *The Structure of a Cell-wall Polysaccharide of Baker's Yeast.*

By D. J. Bell and D. H. Northcote.

The so-called yeast "glucan" has been methylated in an oxygen-free atmosphere. Analysis of the cleavage products on the partition chromatogram shows that the polysaccharide possesses a highly branched structure and that the average unit chain contains nine D-glucose radicals (confirmed by periodate oxidation). 2 : 3 : 4 : 6-Tetramethyl (1 mol.), 2 : 4 : 6-trimethyl (7 mols.), and 4 : 6-dimethyl glucose (1 mol.) were obtained crystalline. It is the first time that this dimethyl sugar has been obtained from material of natural origin after methylation.

Experimental losses were so low that we can claim to have obtained a nearly complete picture of the structure of this polysaccharide.

The cell-wall polysaccharide of baker's yeast has been examined by only a few workers since Salkowski (*Ber.*, **1894**, **27**, 3325) first described it as "yeast cellulose." Salkowski obtained this insoluble carbohydrate by treatment of the yeast cell with 2% potassium hydroxide solution followed by autoclaving of the solid residue with water, and stated that it did not give a blue colour with iodine and yielded glucose and mannose after hydrolysis with dilute sulphuric acid. Zechmeister and Tóth (*Biochem. Z.*, 1934, **270**, 309) treated the yeast with dilute alkali and then rendered the glycogen-like material (which is stained red-brown with iodine) soluble by boiling the product with 3% sulphuric acid. Essentially the same procedure was adopted by Hassid, Joslyn, and McCready (*J. Amer. Chem. Soc.*, 1941, **63**, 295), who used, however, hydrochloric acid in place of sulphuric acid. Both groups of investigators proved that the methylated polysaccharide yielded, as the main cleavage product, 2 : 4 : 6-trimethyl D-glucose, thus showing the presence of a 1 : 3-linkage between the component glucose radicals. Barry and Dillon (*Proc. Roy. Irish Acad.*, 1943, **49**, *B*, 177), by treatment of the polysaccharide with acid periodate, again obtained evidence of the 1 : 3-link since only a small amount of periodate underwent reduction. Furthermore, subsequent bromine oxidation of the periodate-treated material yielded an acid, isolated as its silver salt. From investigation of this substance Barry and Dillon deduced a chain-length of 28 glucose radicals for the yeast glucan. In no case was any evidence obtained whether or not the substance has a branched structure, nor was any "end-group" detected.

The method adopted in the present work was based on the earlier experiments mentioned above, but the "glycogen" component was successfully removed by exhaustion with warm 0·5N-acetic acid. This leaves the insoluble glucan in a non-reducing condition; we find that mineral acid leads to the formation of a reducing product at this stage. Throughout our work we avoided contact with mineral acids and during the methylation of the polysaccharide oxygen was excluded as long as the system was alkaline. We are confident that our material is in fact derived from the cell wall. The washed material isolated from the cytolysis of the yeast, when examined microscopically both in water and after staining with iodine, presented an appearance closely similar to that of intact yeast cells.

Methylation of yeast glucan is difficult. Zechmeister and Tóth (*loc. cit.*) employed as starting-material an acetate made by the action of acetic anhydride and acetic and sulphuric acids. It seems to us that this procedure may lead to unpredictable degradation of the polysaccharide. Hassid *et al.* (*loc. cit.*) carried out direct methylation in presence first of carbon tetrachloride, then of acetone; they completed their etherification using sodium in liquid ammonia (Muskat, *J. Amer. Chem. Soc.*, 1934, **56**, 693, 2449). The use of liquid ammonia and sodium has been criticised by Freudenberg and Boppel (*Ber.*, 1940, **73**, 609) and by Schorigin (*J. Gen. Chem., Russia*, 1944, **14**, 825). Hassid *et al.* methanolysed their methylated material, by prolonged treatment with methanol containing 17% of hydrogen chloride, and distilled the resulting product in a high vacuum, recovering, from 5 g. of methylated polysaccharide, 3·689 g. of 2 : 4 : 6-trimethyl α- + β-methylglucosides. This corresponds with only 67·8% recovery. These authors further carried out viscosity measurements on the methylated polysaccharide applying Staudinger's $K_m = 10^{-3}$ for cellulose and obtained a value *ca.* 6500. As will be seen, we have now shown that yeast glucan possesses a highly branched structure; the application of the constant for the linear polysaccharide is therefore not valid. It may further be noted that Hassid *et al.* deduce, from reasonable evidence, the presence of β-linkages between the component radicals of yeast glucan but they represent the substance in their paper by a structural formula having links of the α-type.

We found that acetylation (pyridine and acetic anhydride) of the partly methylated material

considerably facilitated subsequent etherification. After twenty-six methylations the methoxyl content was 41·5% and was not appreciably raised (41·7%) by five further treatments. In each methylation the losses averaged 1·0—1·1%, the final yield being 55·6%. The methylated glucan was converted into its component radicals by boiling it with methanol containing 2% (w/w) of dry hydrogen chloride and then hydrolysing the resulting mixture of methylglucosides with N-hydrochloric acid at 95—100°. (It should be noted that acid hydrolysis showed that the unsubstituted polysaccharide was composed solely of glucose radicals; see Experimental section.) Analysis of the mixture of methylated glucoses thus obtained by means of Bell's silica–water partition column (*J.*, 1944, 473) gave three crystalline fractions in an aggregate yield of 89·9%. Previous work having shown (Bell, *loc. cit.*; *J.*, 1948, 992) that the recovery of methylated glucoses from the silica columns is of the order of 94% and that the loss on hydrolysis of methylated polysaccharides by N-hydrochloric acid is of the order of 6%, we are confident that we have accounted for *ca.* 100% of the original polysaccharide.

The three crystalline fractions were identified as 2 : 3 : 4 : 6-tetramethyl (1 mol.), 2 : 4 : 6-trimethyl (7 mols.), and 4 : 6-dimethyl D-glucose (1 mol.). Yeast glucan (which must be a polysaccharide of large molecular weight) thus consists of a highly branched structure. Each unit chain must have a mean structure based on about nine glucose radicals; the link between these radicals is of the 1 : 3-type and the inter-chain link is of 1 : 2-type. (It is of course possible that the inter-chain link is 1 : 3, with a 1 : 2-link in the chain itself.) Confirmatory evidence of the chain-length was obtained after oxidation by periodate according to Halsall, Hirst, and Jones (*J.*, 1947, 1399, 1427; *ibid.*, 1948, 27), a value for the chain-length of ten glucose radicals being found. From the small positive rotation (+3°) of the methylated glucan and the large negative rotation of the triacetyl glucan we agree with Hassid *et al.* that the majority of the glycosidic linkages must be of the β-type.

Experimental.

Separation of the Yeast Cell-wall.—Fresh "Encore" baker's yeast (6 kg.) was dispersed in 6% sodium hydroxide solution (4·8 l.), and the whole was heated to 60°, diluted to 40 l. with water, and allowed to cool to room temperature. The insoluble material was collected on the centrifuge, re-suspended in 3% sodium hydroxide solution (10 l.), and kept at room temperature for 3 hours. After dilution with water (20 l.) and again centrifugation, the sludge obtained was suspended in water (10 l.), heated to 80°, and strained through a G 1 Jena filter to remove large particles. After adjustment of the pH to 4·5 the solid was readily filtered off. It was once more digested at 80°, for 2 hours, with 3% sodium hydroxide solution (5 l.) and centrifuged. No carbohydrate was found in the solution (negative Molisch reaction). After adjustment of the pH to 4·5, the solid was collected on a filter and washed first with 2% aqueous acetic acid (10 l.), then with, in turn, ethanol, ether and light petroleum (b. p. 60—80°), 5 l. each. The solid was allowed to dry in the air. The yield of a white powder was 94 g. [Found: N (Kjeldahl), 0·9; P, 0·083%].

Isolation of the Glucan.—Cell-wall material (20 g.) was heated to 75° with 0·5N-acetic acid (700 ml.); the pH of the mixture was *ca.* 2. At 75° the mixture was fluid, but on cooling to 40° it became gelatinous. On centrifugation the gelatinous solid separated, but retained about one-third of the fluid. It was then stirred with water (700 ml.) at 75—80° for an hour and centrifuged. This process was repeated 6 times with 2 l. of water each time. The final supernatant fluid gave no precipitate on addition of ethanol. The gelatinous solid was then treated with 2 volumes of ethanol, centrifuged, washed with more ethanol, and collected on a G 3 Jena filter, with, finally, washing with ether and ligroin, the bulk being thereby greatly decreased; after drying at 100°/0·01 mm., a cream-coloured solid was obtained (7·2 g., 30% of the original cell-wall substance). The glucan (20 g.) was homogenised to a thick paste with water (200 ml.). This was freeze-dried to give a light powder which was used for the subsequent experiments [Found: N (Kjeldahl), 0·42; P, 0·008%].

Identification of Glucose as the Sole Component Radical.—Glucan (2 g.) was dissolved in 72% (w/v) sulphuric acid at room temperature and kept for 240 hours, giving a light brown solution. This was added to water (1 l.) and the whole boiled under reflux for 15 hours. The almost colourless solution was neutralised with barium carbonate and filtered, and the filtrate concentrated to 150 ml. under reduced pressure at 100°. At the same time a control experiment was carried out on cotton cellulose. The hydrolysates were then examined on the paper chromatogram by the procedure of Jermyn and Isherwood (*Biochem. J.*, 1949, 44, 402) using ethyl acetate–pyridine–water as solvents. On development of the chromatogram with ammoniacal silver nitrate a single spot was obtained from each experiment, corresponding exactly in position with a glucose control. Tests for pentoses and uronic acids were negative.

Acetylation of the Glucan.—This was done essentially by the method of Barnett (*J. Soc. Chem. Ind.*, 1921, 40, 253). Freeze-dried polysaccharide (0·5 g.) was suspended in glacial acetic acid (5 ml.) through which chlorine had been passed for a few minutes. After the suspension had been kept for 30 minutes at room temperature, acetic anhydride (5 ml.), containing a little dissolved sulphur dioxide, was added and the whole allowed to react overnight. The mixture was then heated on the boiling water-bath for 2 hours, cooled, and filtered into ice and water (200 ml.). The acetate which separated was filtered off, washed with water, and dried at 80° in a high vacuum (yield, 0·34 g.). This was shaken with a little charcoal in chloroform and the solution filtered through barium carbonate to remove peptised charcoal. The clear chloroform filtrate was boiled with water to remove the organic solvent, and the solid residue

washed and dried as before, to give material (0·2 g.), $[\alpha]_D^{18}$ −62·3° (*c*, 0·6 in chloroform; *l*, 2) (Found: Ac, 44·6. Calc. for $C_{12}H_{16}O_8$: Ac, 44·8%). Hassid *et al.* give $[\alpha]_D$ −72° for material similarly prepared.

Methylation of Glucan.—The freeze-dried polysaccharide (10 g.), suspended in dioxan (200 ml.), was treated, at 40—50°, with methyl sulphate (500 ml.) and 30% sodium hydroxide solution (1 l.), the reagents being added in one-tenth portions at ten-minute intervals, with vigorous stirring, in an atmosphere of nitrogen. After being heated to 80—95°, the solution was acidified to pH 6—7 by addition of acetic acid and the whole distilled under reduced pressure to remove dioxan. The solid which separated was repeatedly washed with boiling water and was then given a second treatment as before. The solid product of the second methylation was dried at 0·01 mm. and then dissolved in pyridine (300 ml.), and acetic anhydride (150 ml.) added. Next morning the mixture was poured into water (2 l.), the product separating as a white solid. The whole aqueous suspension was then concentrated under reduced pressure to a volume of *ca.* 500 ml., heated to *ca.* 95°, and filtered. The solid was washed with boiling water; after being dried in a high vacuum, 10·2 g. were obtained. The material was then soluble in dioxan; it was further subjected to thirty-one methylations in dioxan solution under the conditions described above. The methoxyl content was determined from time to time (Found: OMe, (10 methylations) 36·9, (26 methylations) 41·5, (31 methylations) 41·7%). The final yield was 7·0 g. (55·6%); the average loss per methylation was therefore 1·0—1·1% (Found: N, 0·03; P, 0·00%). The final product had $[\alpha]_D$ +3·3° (*c*, 1·3 in chloroform; *l*, 2).

Cleavage of the Methylated Glucan.—The material (1·4 g.) was refluxed with methanol (50 ml.) containing 2% (w/w) of hydrogen chloride for 18 hours, after which time it had all dissolved. After removal of the hydrogen chloride by treatment with silver carbonate, and of solids by filtration, the resulting solution was evaporated under reduced pressure. The residual syrup, dissolved in N-hydrochloric acid, was heated, under reflux, on the boiling water-bath for a further 18 hours. The solution, freed from hydrochloric acid by excess of silver carbonate in the customary manner, was examined on the paper chromatogram with *n*-butanol–water as solvent (Hirst, Hough, and Jones, *J.*, 1949, 928) and aniline phthalate for development. Spots corresponding to tetra-, tri-, and di-methyl glucoses were found, with R_F values of 0·76, 0·6, and 0·4 respectively. It should be noted that hydrolysis by hydrochloric acid in greater strength than N should be avoided; in some experiments when stronger acid was employed, the tetramethyl glucose fraction was found to contain a non-crystalline component, indistinguishable on the chromatogram from 2 : 3 : 4 : 6-tetramethyl glucose. As this appeared to be a non-reducing material when examined by hypoiodite oxidation (Macleod and Robison, *Biochem. J.*, 1929, **23**, 517), we consider that it is probably a trehalose-like substance (or substances) formed by condensation of two molecules of the trimethyl sugar. Confirmation of this view was obtained by hydrolytic treatment (as described above for methylated glucan) which resolved the substance into trimethyl glucose, as shown by chromatography and hypoiodite reduction.

Separation of the Cleavage Products.—The hydrolysate obtained above was concentrated under reduced pressure to 10 ml. in presence of a little barium carbonate. The methylated sugars were then subjected to chromatographic separation by Bell's method (*J.*, 1944, 473) using a 10-g. column of silica. (The silica was prepared according to Tristram, *Biochem. J.*, 1946, **40**, 721.) Three fractions, all of which crystallised spontaneously, were obtained as follows: Me_4, 0·1594 g.; Me_3, 0·9854 g.; Me_2, 0·1139 g. The molecular ratios corresponded to 1 : 7 : 1, and the aggregate yield was 89·9% of theory.

Identification of the Individual Separated Fractions.—(a) *The tetramethyl fraction.* A sample of the whole fraction (*i.e.*, crystals and syrup) had $[\alpha]_D^{18}$ +90° falling to +83° (*c*, 0·6 in water; *l*, 2). An authentic specimen of 2 : 3 : 4 : 6-tetramethyl glucose examined under the same conditions had $[\alpha]_D^{18}$ +93° falling to +83°. The crystals, after being drained on a tile, melted at 93°. Mixed with authentic material (m. p. 95°) this figure was not appreciably depressed. On the paper chromatogram (solvents: butanol–water) the whole fraction showed a single spot of R_F 0·76, identical with a control sample of 2 : 3 : 4 : 6-tetramethyl glucose (Found: OMe, 52·1. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%).

(b) *The trimethyl fraction.* This after recrystallisation from ether had $[\alpha]_D^{18}$ +84° falling to +70° (*c*, 1·2 in water; *l*, 2). Lake and Peat (*J.*, 1938, 1417) give $[\alpha]_D$ (in water) +98·2° falling to +74·8°, and Hassid *et al.* (*loc. cit.*) give +91·4° falling to +71·4°. The crystals melted at 120° and, on admixture, did not depress the m. p. of authentic 2 : 4 : 6-trimethylglucose (m. p. 115°) (Found: OMe, 41·8. Calc. for $C_9H_{18}O_6$: OMe, 41·2%).

Further proof of the structure of the sugar was obtained by the action of sodium metaperiodate solution; a control with pure 2 : 4 : 6-trimethyl glucose was carried out simultaneously. In neither case, after 25 hours, was any evidence of periodate reduction obtained.

The whole fraction, without recrystallisation, was examined on the paper chromatogram (solvents: butanol–water), the following R_F values being obtained: glucan material, 0·60; authentic 2 : 4 : 6-trimethyl glucose 0·60; 3 : 4 : 6-trimethyl glucose 0·635.

Oxidation by bromine water, followed by conversion of the resulting lactone into the corresponding amide (Lake and Peat, *loc. cit.*), yielded crystals, m. p. 98°, and these, mixed with authentic 2 : 4 : 6-trimethylgluconamide (m. p. 100°) melted at 100°. The amide gave a negative Weerman reaction (Haworth, Peat, and Whetstone, *J.*, 1938, 978).

(c) *The dimethyl fraction.* A sample of the whole fraction had $[\alpha]_D^{18}$ +87·5° (50 minutes) falling to +67·0° (18 hours) (*c*, 0·4 in water; *l*, 2). An authentic specimen of 4 : 6-dimethyl glucose had $[\alpha]_D^{18}$ +93·1° falling to +62·4°. Bell and Synge (*J.*, 1937, 1711) and Bell and Lorber (*J.*, 1940, 453) give respectively +63·6° and +65·7° for $[\alpha]_D$ at equilibrium.

After recrystallisation from ethyl acetate, needles were obtained, having m. p. 155°, not depressed after admixture with authentic 4 : 6-dimethyl glucose, m. p. 158°. On the paper chromatogram (butanol–water) the whole fraction gave a single spot of R_F 0·4, identical in its behaviour with authentic material.

On oxidation with sodium metaperiodate solution a sample of the entire fraction consumed exactly 2 moles of periodate, and yielded 2 moles of formic acid. No formaldehyde was detected by dimedon. Control experiments with authentic 4 : 6-dimethyl glucose, made at the same time, yielded identical results.

End-group Assay of the Glucan by Periodate Oxidation.—This was carried out essentially by the method of Halsall, Hirst, and Jones (*J.*, 1947, 1399, 1427). Since yeast glucan is completely insoluble in water, unlike the polysaccharides used by the above authors, a detailed description of our experiment is given.

To the freeze-dried glucan (493·3 mg.), suspended in water (120 ml.), potassium chloride (5 g.) was added, and the final volume noted. A 10-ml. sample was withdrawn to serve as a control during the subsequent titration. To this control sample, 50% aqueous ethylene glycol (2 ml.) was added. (The glycol was previously distilled over solid potassium hydroxide and then diluted with water, and the pH adjusted to 5.) The suspension was then made up to a volume of 15 ml. and 5-ml. aliquots were titrated, in a stream of carbon dioxide-free air, against 0·01N-sodium hydroxide (methyl-red).

To the main bulk of the original suspension was added sodium periodate solution (0·25M.; 15 ml.), and the whole agitated for 25 hours. The suspension was then allowed to settle and a 10-ml. sample of the supernatant fluid withdrawn and treated in the same way as the control. The whole procedure of agitation and withdrawal of samples at 24-hour intervals was repeated until the production of acid titratable to pH 5 had reached a maximum (280 hours). After this a slight decrease in the acid titre was noticed. The results were:

Time of sampling (hrs.)	24	96	168	240	280	300
Titre (0·01N-NaOH; ml.)	0·48	0·61	0·64	0·66	0·69	0·68

The value 0·69 ml. is equivalent to 12·65 mg. of formic acid and corresponds to a unit chain length of 10·2 glucose radicals.

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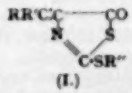
398. *Syntheses in the Penicillin Field. Part IX. A Synthesis of Some Penicillamine Analogues and Attempts to obtain New Types of Penicillins.*

By A. H. COOK, G. HARRIS, J. R. A. POLLOCK, and J. M. SWAN.

The method of synthesising β-phenylcysteine (Cook, Harris, and Heilbron, Studies in the Azole Series, Part V, *J.*, 1948, 1060) was applied to penicillamine (Cook, Harris, Heilbron, and Shaw, "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 458). Improved methods of synthesis led to β-(*p*-chlorophenyl)cysteine and β-(*p*-methoxyphenyl)cysteine, which, like the β-phenyl compound, failed to afford penicillin-like activity under standardised conditions. Attempts to apply the synthesis of penicillin due to du Vigneaud and his co-workers to thiazolone instead of oxazolone derivatives were unsuccessful.

THE condensation of 2-ethylthiothiazolin-5-one with acetone in place of benzaldehyde was expected to yield the thiazolinone (I; R = R′ = Me, R″ = Et). Reaction of *N*-dithiocarbethoxyglycine (II) with acetone and acetic anhydride gave only the 2-ethylthiothiazolin-5-one, characterised as *N*-dithiocarbethoxyglycine anilide, and as *N*-benzylthioureidoacetbenzylamide, but when sodium acetate was added to the mixture as a condensing agent the reaction proceeded as expected to give 2-ethylthio-4-*iso*propylidenethiazolin-5-one (I; R = R′ = Me, R″ = Et). The last compound was characterised by its reaction with benzylamine forming the thiohydantoin (III), a transformation analogous to that undergone by 2-ethylthio-4-benzylidene-



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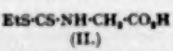

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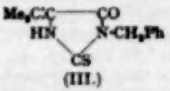
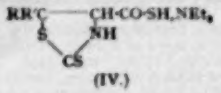


(III.)

thiazolin-5-one (Cook, Harris, and Heilbron, *J.*, 1948, 1060). The compound (I; R = R′ = Me, R″ = Et) with hydrogen sulphide in methanolic triethylamine gave the triethylammonium salt (IV; R = R′ = Me) in good yield. It had been found previously that the hydrolysis of (IV; R = Ph, R′ = H) or the thio-acid with concentrated hydrochloric acid proceeded anomalously. The product obtained did not give the ferric chloride, nitroprusside, or ninhydrin reaction expected for β-phenylcysteine, and the properties and analysis of the product prompt its formulation as 5-phenylthiazole-4-carboxylic acid hydrochloride (V), formed from the thiothiazolidone (IV; R = Ph, R′ = H) by elimination of the elements of hydrogen sulphide. Obviously the compound (IV; R = R′ = Me) could not undergo any comparable change, and treatment with hydrochloric acid gave 2-thio-5 : 5-dimethylthiazolidone-4-carboxylic acid which

was converted into penicillamine by reductive fission with aluminium and acid (Cook, Heilbron, and Shaw, CPS 311; "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 458).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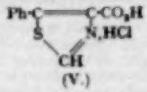
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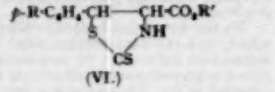
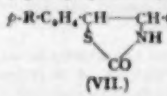

(VI.)

The synthesis of other amino-mercapto-acids by this route were not pursued since more convenient routes utilising the parent 2-mercaptothiazolin-5-one in place of the ethylthio-derivatives were devised (cf. Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337), although the compounds (I; R = *p*-C_6H_4·NO_2, R′ = H, R″ = Et) and (I; R = *p*-C_6H_4·OAc, R′ = H, R″ = Et) were prepared as possible intermediates for such syntheses.

2-Mercaptothiazolin-5-one was found to condense readily with anisaldehyde, *p*-acetoxybenzaldehyde, and *p*-chlorobenzaldehyde, among others, in acetic acid containing a trace of morpholine to yield 2-mercapto-4-*p*-methoxybenzylidene-, -4-*p*-acetoxybenzylidene-, and -4-*p*-chlorobenzylidene-thiazolin-5-one (I; R = R″ = H, R′ = *p*-C_6H_4·OMe, *p*-C_6H_4·OAc, *p*-C_6H_4Cl respectively). These compounds were well characterised as their 2-methylthio-derivatives (I; R = H, R″ = SMe, R′ = *p*-C_6H_4·OMe, *p*-C_6H_4·OAc, *p*-C_6H_4Cl respectively) by reaction with methyl sulphate and alkali, and the chloro- and acetoxy-compounds were degraded with phosphorus and hydriodic acid to β-(*p*-chlorophenyl)alanine and tyrosine respectively (cf. Billimoria and Cook, *J.*, 1949, 2323).

Treatment of the thiazolinones (I; R = R″ = H, R′ = *p*-C_6H_4·OMe and *p*-C_6H_4Cl) with methanolic sodium hydroxide gave the acids (VI; R′ = H, R = OMe or Cl) and with methanolic sodium methoxide gave the methyl esters (VI; R′ = Me, R = OMe or Cl) as in previous similar experiments. The acetoxy-compound behaved abnormally with alkalis, however, and to obtain isomerisation of the arylidenethiazolinone to the 2-mercapto-Δ^2-thiazoline or the thiothiazolidone system recourse was had to the method used above for the thiazolinone (I; R = R′ = Me, R″ = Et). When this acetoxy-compound was treated with hydrogen sulphide in methanolic triethylamine the compound (IV; R = *p*-C_6H_4·OAc, R′ = H) was obtained in good yield, and this salt was converted into the carboxylic acid (VI; R = OH, R′ = H) by means of concentrated hydrochloric acid. Hydrolysis of the acids (VI; R′ = H, R = OH, OMe, or Cl) with concentrated hydrochloric acid by the method used for the preparation of β-phenylcysteine (Cook, Harris, and Heilbron, *loc. cit.*) was in no case found to lead to the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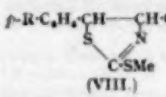
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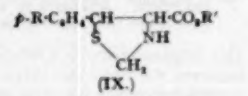

(IX.)

amino-mercapto-acid, although the hydroxy-compound was isolated from the methoxy-compound in some instances. The difficulty encountered here may well have been caused by partial thiazole formation as encountered above. An effort to overcome these difficulties was made by preparing 5-*p*-methoxyphenyl-2-thiazolidone-4-carboxylic acid (VII; R = OMe) by the oxidation of (VI; R = OMe, R′ = H) with alkaline hydrogen peroxide. The compound (VII; R = H) had been shown to yield β-phenylcysteine on hydrolysis (Cook, Harris, and Heilbron, *loc. cit.*), but (VII; R = OMe) gave no amino-mercapto-acid on such treatment. Reductive degradation of (VI; R = OMe, R′ = H) with aluminium and acid (Cook, Heilbron, and Shaw, CPS 311; *op. cit.*, p. 458) or with tin and acid was likewise unsuccessful.

By this time the discovery of a new method of fission of the thiothiazolidone ring system had been found in another series of compounds containing the amide group in place of the CO_2R groups discussed here (cf. Cook, Hunter, and Pollock, *J.*, in press) and consisted essentially in methylating the 2-mercapto-group of the thiothiazolidones (such as VI) (which may be regarded as 2-mercapto-Δ^2-thiazolines) to give compounds of type (VIII) (cf. Cook, Harris, and Heilbron, *loc. cit*), which were then reduced with aluminium amalgam with loss of methanethiol to form the thiazolidines (IX). Fission of the latter compounds was readily accomplished with mercuric chloride to yield the required amino-mercapto-acids.

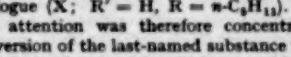
Application of the technique to the acids (VI; R = OMe or Cl, R′ = H), which were methylated with diazomethane, gave the methyl esters of the methylthio-compounds (VIII; R = OMe or Cl), reduction of which with aluminium amalgam in methanol gave the thiazolidines (IX; R′ = Me, R = OMe or Cl), the methoxy-compound being characterised as

its 3-acetyl derivative. Hydrolysis of (IX; R = OMe, R′ = Me) with hydrochloric acid gave no amino-mercapto-acid, but the acid (IX; R = OMe, R′ = H) isolated as its hydrochloride. Fission of this substance with boiling ethanolic mercuric chloride gave only the disulphide of β-(*p*-methoxyphenyl)cysteine, isolated as its oxalate, whereas fission of both (IX; R = OMe, R′ = Me) and (IX; R = Cl, R′ = Me) with hot aqueous mercuric chloride gave β-(*p*-methoxyphenyl)cysteine and β-(*p*-chlorophenyl)cysteine, respectively, as their hydrochlorides.

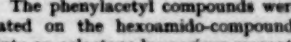
A series of three β-arylcysteines was thus available for attempts to obtain new penicillins.

Attempts to obtain Penicillin-like Materials from β-Phenylcysteines.—When this research was initiated, the thiazolidine-oxazolone structure (cf. *op. cit.*) was widely accepted as representing penicillin, and many attempts were made to obtain this, and later the thiazolidine β-lactam structure, by preparing azlactones from penicilloic acids, and by condensing ethoxymethyleneoxazolones with penicillamine. Accordingly, the preparation of penicilloic acid analogues (X) from β-phenylcysteine was undertaken.

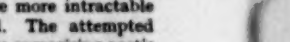
Condensation of β-phenylcysteine hydrochloride with ethyl α-formylphenaceturate and with α-formylhexoamidoacetate gave the thiazolidines (X; R′ = Et, R = CH_2Ph or *n*-C_6H_{11}), isolated first as the hydrochlorides. Hydrolysis of (X; R′ = Et, R = *n*-C_6H_{11}) with one equivalent of sodium hydroxide, isolating the product *via* its lead salt, gave the penicilloic acid analogue (X; R′ = H, R = *n*-C_6H_{11}). The phenylacetyl compounds were more intractable and attention was therefore concentrated on the hexoamido-compound. The attempted conversion of the last-named substance into an azlactone by various reagents comprising acetic anhydride alone and in admixture with pyridine or triethylamine at various temperatures for various times, carbon suboxide, acetic anhydride in methyl oxalate, and benzoyl chloride in pyridine gave no significantly bacteriostatic products (tested by the plate method).



(X.)



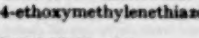
(XI.)



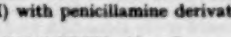
(XII.)

Some early attempts were made to condense β-phenylcysteine with 2-benzyl-4-ethoxymethylene(or -hydroxymethylene)benzyloxazolone in acetic anhydride–pyridine–sodium acetate or buffered dioxan solutions at room temperature or 60°, but again no active products were obtained. Later, it was shown by du Vigneaud and his co-workers (*J. Biol. Chem.*, 1948, **176**, 917) that penicillamine and other amino-mercapto-acids condensed with 2-benzyl-4-ethoxymethyleneoxazolone and other oxazolones to yield penicillins, albeit in very small yield. The application of their conditions to the condensation of β-phenylcysteine with 2-benzyl-4-ethoxymethyleneoxazolone, however, yielded no bacteriostatic product, and similar reactions with β-(*p*-methoxyphenyl)cysteine and β-(*p*-chlorophenyl)cysteine likewise failed to give bacteriostatic activity. Although the optimum conditions for penicillamine might not have been those for the β-arylcysteines with regard to these condensations, and optically inactive arylcysteines were used, it seems significant that these compounds gave rise to no detectable activity, particularly as β-benzyl-β-methylcysteine (Cook and Pollock, *J.*, in press) afforded activity on condensation with the above ethoxymethylene compound.

Attempts to extend the Above Type of Condensation.—It was shown previously (Cook, Harris, Heilbron, and Shaw, *J.*, 1948, 1056) that penicillamine or its methyl ester condensed readily with mercapto(or ethylmercapto)-2-benzyl-4-ethoxymethylenethiazolin-5-one to form analogues of penicillenic acid (XI; R = CH_2Ph or Et, R′ = H or Me), but that these compounds would not undergo closure of the thiazolidine ring. Experiments were also made on the condensation of 2-mercapto-4-ethoxymethylenethiazolin-5-one (XII) with penicillamine derivatives in order



(XIII.)

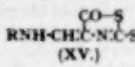


(XIV.)

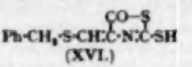
to obtain a penicillenic acid analogue (XI; R = H, R′ = H or Me), which might be rearranged with loss of carbon disulphide to give the 6-aminothiazolidine-β-lactam structure (XIII), the parent structure of the penicillins, or a thiazolidinyl-thiazolinone structure (XIV), which might undergo self-acylation with loss of carbon disulphide to form (XIII). Presumably (XIV) would be an intermediate in the conversion of (XI; R = H) into (XIII), just as it may be supposed that the thiazolidine-oxazolone structure is intermediate in the transformation of penicillenic acid into penicillin (cf. du Vigneaud and his co-workers, *loc. cit.*).

Model reactions showed that the penicillenic acid analogue would be the most likely product of such condensations. Thus, glycine ethyl ester and 2-mercapto-4-ethoxymethylenethiazolin-

5-one in aqueous acetone afforded 2-*mercapto*-4-(*carbethoxymethylaminomethylene*)*thiazolin*-5-*one* (XV; R = $EtO_2C{\cdot}CH_2$). In the same way, glycine sodium salt, DL-alanine methyl ester, and *S*-benzylpenicillamine sodium salt gave 2-mercapto-4-(carboxymethylaminomethylene)- (XV; R = $HO_2C{\cdot}CH_2$), -4-(1′-carbomethoxypropylaminomethylene) (XV; R = $CHMe{\cdot}CO_2Me$), and



(XV.)

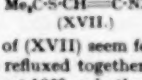


(XVI.)

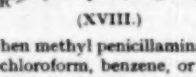
-4-(1′-carboxy-2′-benzylthio-2′ : 2′-dimethylpropylaminomethylene)-thiazolin-5-one [XV; R = $Me_2C(S{\cdot}CH_2Ph){\cdot}CH{\cdot}CO_2H$] respectively. These compounds showed characteristic ultra-violet absorption maxima at 2450 and 3370—3460 A. Reaction between thiols and the ethoxymethylene compound appeared to be more sluggish, the latter reacting with toluene-ω-thiol only in the presence of a catalyst (triethylamine) to form two isomers of 2-mercapto-4-benzylthiomethylenethiazolin-5-one (XVI), presumably *cis*- and *trans*- about the exocyclic double bond.

When penicillamine (as its sodium salt or methyl ester) was allowed to react with the sodium salt of (XII) in water, or with (XII) in ethanol, only amorphous, easily oxidised products were obtained. With penicillamine in ethanol, no reaction occurred, and in pyridine the product was an oil, whereas in aqueous Cellosolve the amorphous product was rapidly oxidised to a red tar. These difficulties were possibly caused in part by reaction of (XII) with the thiol group of penicillamine and, in part, by ring-opening of the thiazoline by the amino-group as experience had shown was feasible. Accordingly, reaction of (XV) with derivatives of 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid was attempted, but the thiazolidine proved insufficiently basic to undergo the desired reaction in hot acetone, and, in the presence of triethylamine, only an amorphous product was obtained.

Another approach to (XIII) lay in attempts to obtain the compound (XVII), which on rearrangement *via* a seven-membered ring structure could give (XIII). The protective effect of salt formation on amino-groups appeared to be applicable to this case. Thus, Ratner and Clarke (*J. Amer. Chem. Soc.*, 1937, **59**, 200) in a study of the rate of formation of thiazolidine-4-carboxylic acid from cysteine and formaldehyde were able to show that in acid solution initial reaction occurred on the sulphur atom, and Armstrong and du Vigneaud (*J. Biol. Chem.*, 1948, **173**, 749) treated a variety of aldehydes and ketones with cysteine in 6N-hydrochloric acid to obtain the compounds (XVIII) instead of thiazolidines. The stability of (XII) to acids made



(XVII.)



(XVIII.)

the preparation of (XVII) seem feasible. However, when methyl penicillaminate hydrochloride and (XII) were refluxed together for long periods in chloroform, benzene, or ethyl acetate, or heated in anisole at 100°, only the unchanged reactants were recovered. At higher temperatures (refluxing anisole) decomposition occurred, and reaction in methanolic hydrogen chloride or 6N-hydrochloric acid failed to bring about the desired condensation. Extension of such reactions to methyl *N*-acetylpenicillaminate or *N*-phenylacetylpenicillaminate, and *N*-carbobenzyloxypenicillamine was equally unsuccessful. Similar attempts to cause *N*-phenylthiocarbonylpenicillamine to react with oxazolones are described in a later paper.

Experimental.

Penicillamine Analogues.—*N*-Dithiocarbethoxyglycine (2·5 g.), acetone (2·0 g.), and acetic anhydride (6 c.c.) were heated on the steam-bath for 15 minutes, solvents were removed *in vacuo*, and the residue was distilled at 40° in a high vacuum, to give a pale yellow oil. A portion reacted vigorously with ethereal benzylamine. The product, recrystallised from chloroform–light petroleum, gave *N*-benzylthioureidoacetbenzylamide as needles, m. p. 145—146° (Found: C, 65·7; H, 6·1; N, 13·5. Calc. for $C_{17}H_{18}ON_2S$: C, 65·2; H, 6·1; N, 13·4%). A portion of the oil with ethereal aniline gave *N-dithiocarbethoxyglycine anilide*, which separated from chloroform as white laths, m. p. 159—160° (decomp.) (Found: C, 52·3; H, 5·8; N, 11·0. $C_{11}H_{14}ON_2S_2$ requires C, 52·0; H, 5·6; N, 11·0%).

N-Dithiocarbethoxyglycine (10 g.), acetone (26 g.), acetic anhydride (20 g.), and anhydrous sodium acetate (5 g.) were refluxed together for 3½ hours. When the product was worked up by dissolution in ether and removal of acidic material with sodium hydrogen carbonate an oil was obtained, distillation of which gave 2-ethylthio-4-*iso*propylidenethiazolin-5-one (I; R = R′ = Me, R″ = Et) (5·5 g.), b. p. 110—115°/0·2 mm. (Found: N, 6·5. Calc. for $C_8H_{11}ONS_2$: N, 7·0%). With ethereal benzylamine, a portion of the oil gave 1-*benzyl*-4-*isopropylidene*-2-*thiohydantoin* (III), which crystallised from chloroform–light petroleum as white needles, m. p. 201° (Found: C, 63·4; H, 5·8. $C_{13}H_{14}ON_2S$ requires C, 63·4; H, 5·7%).

Triethylammonium 2-thio-5-phenylthiazolidone-4-thiocarboxylate (IV; R = H, R′ = Ph) (6·8 g.)

was heated for 16 hours at 90—100° with concentrated hydrochloric acid (35 c.c.) in a sealed tube. After cooling to 0°, the crystalline precipitate was removed, washed with *iso*propanol and water, and recrystallised several times from aqueous ethanol. *5-Phenylthiazole-4-carboxylic acid hydrochloride* (V) separated as clear, hexagonal plates, m. p. 225° (decomp.) (Found: C, 50·1; H, 3·7; N, 6·1. $C_{10}H_8NClS$ requires C, 49·8; H, 3·4; N, 5·9%). It gave no colour with ninhydrin or alkaline sodium nitroprusside, and a red precipitate with aqueous ferric chloride. From the filtrates, β-phenylcysteine hydrochloride was obtained (31% in one experiment). Hydrolysis of the free thiocarboxylic acid also gave a mixture of the thiazole and β-phenylcysteine.

N-Dithiocarbethoxyglycine (3·6 g.), *p*-hydroxybenzaldehyde, and acetic anhydride (15 c.c.) were heated together on the steam-bath for 10 minutes. Solvents were removed *in vacuo*, finally over potassium hydroxide. The sludge was treated with a small quantity of acetone, and the orange solid washed with *n*-amyl alcohol and with light petroleum, and recrystallised from acetone–water, *2-ethylthio-4-p-acetoxybenzylidenethiazolin-5-one* (I; R = H, R″ = Et, R′ = *p*-AcO·C_6H_4) (19%) separating as pale orange, rhombic plates, m. p. 108—110° (Found: C, 54·8; H, 4·5; N, 4·7. $C_{14}H_{13}O_3NS_2$ requires C, 54·7; H, 4·3; N, 4·6%). *N*-Dithiocarbethoxyglycine (1·8 g.), *p*-nitrobenzaldehyde (1·5 g.), and acetic anhydride (5 c.c.) were heated together at 100° for 3 minutes. The product (1·8 g.), which crystallised on cooling, was washed with light petroleum and ethanol and recrystallised from ethanol, *2-ethylthio-4-p-nitrobenzylidenethiazolin-5-one* (I; R = H, R″ = Et, R′ = *p*-NO_2·C_6H_4) separating as yellow needles, m. p. 161° (Found: C, 49·4; H, 3·7; N, 9·4. $C_{12}H_{10}O_3N_2S_2$ requires C, 49·0; H, 3·4; N, 9·5%). The filtrates gave a further 0·2 g.

β-(p-Methoxyphenyl)cysteine and Derivatives of β-(p-Hydroxyphenyl)cysteine.—*p*-Anisaldehyde (20 g.) was dissolved in boiling acetic acid (150 c.c.) containing 2-mercaptothiazolin-5-one (20 g.), and morpholine (10 drops) added. After 2 hours at room temperature, the yellow crystalline product (30 g.) was filtered off and washed with acetic acid and water; a further crop (2 g.) separated on dilution of the filtrate with water (500 g.). Recrystallised from acetic acid, *2-mercapto-4-p-methoxybenzylidenethiazolin-5-one* (I; R = R″ = H, R′ = *p*-C_6H_4·OMe) separated as yellow needles, m. p. 212° (decomp.) (Found: C, 52·2; H, 3·5; N, 5·8. $C_{11}H_9O_2NS_2$ requires C, 52·6; H, 3·6; N, 5·6%). This compound (1 g.) was taken up in 0·5*N*-potassium hydroxide (8 c.c.), methyl sulphate (0·5 g.) added, and the mixture shaken for 10 minutes. The yellow solid (1 g.) was recrystallised from a small volume of ethanol, *2-methylthio-4-p-methoxybenzylidenethiazolin-5-one* separating as long yellow needles, m. p. 124° (Found: N, 5·2. $C_{12}H_{11}O_2NS_2$ requires N, 5·3%).

2-Mercapto-4-*p*-methoxybenzylidenethiazolin-5-one (5 g.) was dissolved in hot methanolic sodium methoxide (1 g. of sodium per 30 c.c.) and kept for 1 hour. It was poured into ice-cold 2*N*-hydrochloric acid (150 c.c.), and the mixture kept for 1 hour. The gum was taken up in acetone and crystallised by the cautious addition of water at 0°. Next morning the product (2·8 g.) was recrystallised from acetone–water, *methyl 2-mercapto-5-p-methoxyphenylthiazoline-4-carboxylate* (VI; R = OMe, R′ = Me) forming pale yellow needles, m. p. 108° (Found: C, 50·7; H, 4·7. $C_{12}H_{11}O_3NS_2$ requires C, 50·9; H, 4·6%).

2-Mercapto-4-*p*-methoxybenzylidenethiazolin-5-one (37 g.) was added to a hot solution of sodium hydroxide (11 g.) in methanol (250 c.c.). After 2·5 hours at room temperature the solution was filtered through glass wool, diluted with water (1 l.), and acidified with concentrated hydrochloric acid. The oil crystallised when seeded. The product (28 g.) was recrystallised from acetone–water and boiling water, to give *2-mercapto-5-p-methoxyphenylthiazoline-4-carboxylic acid* as colourless, hexagonal plates, m. p. 149° (decomp.) (Found: C, 49·4; H, 4·3. $C_{11}H_{11}O_3NS_2$ requires C, 49·1; H, 4·1%).

Methyl 2-mercapto-5-*p*-methoxyphenylthiazoline-4-carboxylate (2 g.) in 10% aqueous sodium hydroxide (10 c.c.) was treated with 20-vol. hydrogen peroxide (10 c.c.). After 3 hours the solution was acidified with concentrated hydrochloric acid and the sticky solid crystallised from aqueous methanol (yield, 1·2 g.; m. p. 135°). Crystallised from water, *5-p*-methoxyphenyl-2-thiazolidone-4-carboxylic acid separated as colourless rods, m. p. 138°.

β-(p-Chlorophenyl)cysteine.—*p*-Chlorobenzaldehyde (McEwen, *Org. Synth.*, Coll. Vol. II, 1943, p. 133) (18 g.) and 2-mercaptothiazolin-5-one (16 g.) were condensed in hot acetic acid (250 c.c.) containing morpholine (10 drops). *2-Mercapto-4-p-chlorobenzylidenethiazolin-5-one* (18 g.) was collected next morning, and recrystallised from acetic acid as orange needles, m. p. 250° (decomp.) (Found: C, 47·3; H, 2·6. $C_{10}H_4ONClS_2$ requires C, 47·0; H, 2·4%). This compound (1 g.) in 2*N*-sodium hydroxide (2·5 c.c.) was methylated by methyl sulphate (0·4 c.c.). The *2-methylthio*-derivative (1 g.) separated from methanol as golden needles, m. p. 145—146° (Found: C, 49·8; H, 3·0. $C_{11}H_6ONClS_2$ requires C, 48·9; H, 3·0%). The original mercaptothiazolinone (2 g.) in acetic acid (25 c.c.) and 40% hydriodic acid (10 c.c.) was heated under reflux for 4 hours with red phosphorus (2 g.). After cooling and filtration, the solution was evaporated *in vacuo*. The residue in water (15 c.c.) was repeatedly extracted with benzene to remove iodine. The aqueous layer was neutralised with aqueous ammonia (2%) and evaporated to dryness.

2-Mercapto-4-p-acetoxybenzylidenethiazolin-5-one (I; R = R″ = H, R′ = *p*-AcO·C_6H_4) (16 g.) separated from acetic acid as yellow needles, m. p. 180°, resolidifying and remelting at 196° (Found: C, 51·9; H, 3·1; N, 5·0. $C_{12}H_9O_4NS_2$ requires C, 51·6; H, 3·25; N, 5·0%). A portion (1 g.) in 0·5*N*-potassium hydroxide (9 c.c.) was methylated with methyl sulphate (0·5 g.). The yellow product (1 g.) was recrystallised from methanol, *2-methylthio-4-p-acetoxybenzylidenethiazolin-5-one* separating with m. p. 114° (Found: C, 53·6; H, 3·9. $C_{13}H_{11}O_4NS_2$ requires C, 53·25; H, 3·75%).

A suspension of 2-mercapto-4-*p*-acetoxybenzylidenethiazolin-5-one (5 g.) in methanol (20 c.c.) was treated with triethylamine (2 g.), dissolution occurring. Hydrogen sulphide was passed into the solution for 12 hours, and the liquid was then diluted with ether (250 c.c.) and seeded. The product (2·5 g.), m. p. 120—124°, was recrystallised from ethyl acetate, *triethylammonium 2-mercapto-5-p-acetoxyphenyl-Δ⁴-thiazoline-4-thiocarboxylate* (IV; R = AcO, R′ = $NHEt_3$) separating as colourless prisms, m. p. 127—128° (decomp.) (Found: C, 52·7, 52·7; H, 6·4, 5·5; N, 6·9. $C_{19}H_{24}O_3N_2S_3$ requires C, 52·2; H, 6·3; N, 6·8%).

(*a*) 2-Mercapto-5-*p*-hydroxyphenylthiazoline-4-carboxyamide (1 g.) (Cook, Hunter, and Pollock, *J.*, in press) was refluxed for 1 hour with 2*N*-sodium hydroxide (10 c.c.), ammonia being evolved.

Acidification of the solution gave *2-mercapto-5-p-hydroxyphenylthiazoline-4-carboxylic acid* (0·1 g.), which, recrystallised from water, separated as pale yellow, rhombic plates, m. p. 196° (Found: C, 47·5; H, 3·7. $C_{10}H_9O_3NS_2$ requires C, 47·1; H, 3·6%).

(*b*) The triethylammonium salt above (2 g.) in ethanol (5 c.c.) was treated with concentrated hydrochloric acid (2 c.c.). The solvent was removed and the gum extracted with a mixture of ethyl acetate (20 c.c.) and water (10 c.c.). The aqueous layer was re-extracted with ethyl acetate (10 c.c.) and the combined extracts were evaporated to give a yellow oil which was digested on the steam-bath for 3 hours with concentrated hydrochloric acid (10 c.c.). The solution was diluted to 30 c.c. with water and extracted with ethyl acetate (3 × 20 c.c.). The solution was filtered from amorphous material (probably the derived diketopiperazine), dried, and evaporated to small bulk and light petroleum (b. p. 60—80°) was cautiously added. The above acid (0·7 g.) separated as colourless plates containing ethyl acetate of crystallisation and having m. p. 122° (decomp.) (Found: C, 49·0, 48·9; H, 4·8, 4·8; N, 4·7. $C_{10}H_9O_3NS_2,C_4H_8O_2$ requires C, 49·0; H, 5·0; N, 4·1%). When kept at 100°/14 mm. for 18 hours it became sticky and, when recrystallised from hot water (charcoal), separated as plates, m. p. 190—194°, undepressed on admixture with the material obtained as recorded under (*a*).

2-Mercapto-5-*p*-methoxyphenylthiazoline-4-carboxylic acid (20 g.), suspended in ether (50 c.c.), was treated with diazomethane (10 g.) in ether (500 c.c.) slowly with stirring. After 2 hours ether was removed, leaving a viscous oil. The latter in methanol (1 l.) was reduced with aluminium amalgam (30 g.). After reaction was complete the hot solution was filtered and the alumina washed with hot methanol (2 × 250 c.c.). The filtrate was evaporated until cloudy and diluted with water. The product (6 g.) was recrystallised from aqueous methanol, giving *methyl 5-p-methoxyphenylthiazolidine-4-carboxylate* (IX; R = MeO, R′ = Me) as needles, m. p. 81° (Found: C, 56·7; H, 6·0; N, 4·8. $C_{12}H_{15}O_3NS$ requires C, 56·9; H, 6·0; N, 5·5%). Warming this with acetic anhydride gave the *acetyl* derivative, which crystallised from aqueous methanol as laths, m. p. 94—95° (Found: C, 56·8; H, 6·1. $C_{14}H_{17}O_4NS$ requires C, 57·0; H, 5·8%). Hydrolysis of the thiazolidine ester (0·5 g.) with 4*N*-hydrochloric acid (20 c.c.) during 13 hours, followed by evaporation to dryness and stirring of the residue with dry ether gave *5-p-methoxyphenylthiazolidine-4-carboxylic acid hydrochloride* (0·4 g.) which recrystallised from methanol–ether, whereafter it had m. p. 193—196° (decomp.) (Found: C, 47·5; H, 5·4; N, 4·7. $C_{11}H_{14}O_3NClS$ requires C, 47·9; H, 5·1; N, 5·1%). The hydrochloride (0·3 g.) was dissolved in water (2 c.c.), and the product (0·2 g.) collected. Recrystallised from water the resultant free *acid* separated as prisms, m. p. 210° (decomp.) (Found: C, 55·1; H, 5·7; N, 6·3. $C_{11}H_{13}O_3NS$ requires C, 55·5; H, 5·9; N, 5·9%).

Methyl *5-p*-methoxyphenylthiazolidine-4-carboxylate (2·5 g.) in methanol (10 c.c.) was added to mercuric chloride (5 g.) in methanol (300 c.c.). The clear mixture was refluxed for 1 hour, concentrated, and decomposed with hydrogen sulphide. Evaporation of the filtrate gave a yellow gum which was treated with hot acetone for 5 minutes, the solution evaporated, and the residue stirred with aqueous sodium hydrogen carbonate. The yellow oil was extracted into ether and dried, and oxalic acid added. After being kept overnight the product (0·7 g.) was separated and recrystallised from methanol–ether–light petroleum, *di-(2-amino-2-carbomethoxy-1-p-methoxyphenylethyl) disulphide di(hydrogen oxalate)* forming needles, m. p. 148° (Found: C, 47·0; H, 5·2; N, 3·8. $C_{26}H_{32}O_{14}N_2S_2$ requires C, 47·3; H, 4·9; N, 4·2%).

The technique described below for *β-(p*-chlorophenyl)cysteine was applied to the preparation of *β-(p-methoxyphenyl)cysteine hydrochloride* from methyl *5-p*-methoxyphenylthiazolidine-4-carboxylate. The product was recrystallised by the slow addition of ether to a solution in dry ethanol; it separated as colourless prisms, m. p. 166° (Found: C, 45·0; H, 5·6; N, 4·9. $C_{10}H_{13}O_3NS,HCl$ requires C, 45·5; H, 5·4; N, 5·3%). It gave an indigo-blue colour with ferric chloride in neutral solution, and a red-purple colour with ninhydrin.

p-Acetoxybenzaldehyde (11 g.) (cf. Chattaway, *J.*, 1931, 2495) was added to a hot solution of 2-mercaptothiazolin-5-one. Piperidine (4 drops) was added, and after 2 hours the product was filtered off and washed with acetic acid, the residue stirred with water, and the product (0·8 g.) removed and recrystallised from water (charcoal). *β-(p*-Chlorophenyl)alanine separated as hexagonal tablets, m. p. 253° (decomp.) (Found: C, 54·3; H, 5·6; N, 6·7. Calc. for $C_9H_{10}O_2NCl$: C, 54·1; H, 5·0; N, 7·0%). The original mercaptothiazolinone (30 g.) was dissolved in hot methanolic potassium hydroxide (9 g./100 c.c.) and the solution kept for 0·5 hour. It was diluted to 500 c.c. and acidified. After 12 hours at 0° the aqueous layer was decanted and the oil dissolved in ethyl acetate (100°) and dried (solution *A*). A portion of *A* was extracted with aqueous sodium hydrogen carbonate, and the aqueous solution washed with ethyl acetate. Acidification gave an oil, extracted into ethyl acetate and dried. Addition of light petroleum (b. p. 40—60°) precipitated *2-mercapto-5-p-chlorophenylthiazoline-4-carboxylic acid* (VI; R = Cl, R′ = H), which recrystallised as needles, m. p. 176° (Found: C, 43·8; H, 3·2; N, 5·3. $C_{10}H_8O_3NClS_2$ requires C, 43·9; H, 3·0; N, 5·1%). Solution *A* was treated with diazomethane (11 g.) in ether (300 c.c.). After 3 hours, evaporation of solvents gave a yellow oil, which was taken up in methanol (400 c.c.) and reduced in the usual way with aluminium amalgam (20 g.). The methanol filtrate was evaporated to small bulk and diluted with water (1 l.). The product (10·2 g.), m. p. 110°, was recrystallised from aqueous methanol to give *methyl 5-p-chlorophenylthiazolidine-4-carboxylate* (IX; R = Cl, R′ = Me) as needles, m. p. 114—115° (Found: C, 50·8; H, 4·7; N, 5·2. $C_{11}H_{12}O_2NClS$ requires C, 51·3; H, 4·7; N, 5·4%).

The above thiazolidine (1 g.) in ethanol (10 c.c.) was heated to boiling and diluted with hot water (100 c.c. at 60°). The milky liquid was added immediately to hot aqueous mercuric chloride (2·5 g./100 c.c.). Formaldehyde was evolved, a white curd being precipitaed. After cooling, the filtered curd was thoroughly washed, suspended in *N*-hydrochloric acid, and decomposed with hydrogen sulphide. The filtrate was evaporated to dryness and the residue, m. p. 170—173° (decomp.), recrystallised from ethanol–ether; *β-(p-chlorophenyl)cysteine hydrochloride* separated as colourless plates, m. p. 177° (decomp.) (Found: C, 39·7; H, 4·8; N, 5·1. $C_9H_{11}O_2NCl_2S$ requires C, 40·0; H, 4·1; N, 5·2%). It gave a purple colour with ferric chloride in neutral solution, and a red-purple colour with ninhydrin.

Attempts to obtain Penicillin-like Materials from β-Phenylcysteines.—(*a*) β-Phenylcysteine hydrochloride (2·3 g.) and ethyl α-formylhexoamidoacetate (2·6 g.) were heated for 10 minutes at 100° with a few drops of methanol, whereafter the melt gave no colour with ferric chloride. The resin was triturated with dry ether containing a little hydrogen chloride, and the white solid (2·6 g.) kept under dry ether until it no longer became sticky on exposure to air. Several recrystallisations from methanol–ether yielded *5-phenyl-2-hexoamidocarbethoxymethylthiazolidine-4-carboxylic acid hydrochloride* (X; R = C_5H_{11}, R′ = Et) as white needles, m. p. 179° (decomp.) (Found: C, 53·5; H, 6·6; N, 6·8. $C_{20}H_{29}O_5N_2ClS$ requires C, 54·0; H, 6·6; N, 6·3%). On dissolution of this in aqueous sodium hydrogen carbonate, acidification, and extraction with chloroform, *5-phenyl-2-hexoamidocarbethoxymethylthiazolidine-4-carboxylic acid* was obtained and had m. p. 135°, after recrystallisation from ethanol–water (Found: C, 58·6; H, 7·2; N, 6·3. $C_{20}H_{28}O_5N_2S,H_2O$ requires C, 56·3; H, 7·1; N, 6·6%). β-Phenylcysteine (1·0 g.) was heated for 12 minutes at 100° with ethyl α-formylphenaceturate (1·5 g.) and methanol (1 c.c.). After 4 minutes a few drops of methanolic hydrogen chloride were added and further heating conducted in a vacuum. The pale-orange resinous product was rendered solid as above, and the product (1·7 g.) dried *in vacuo* and purified by precipitation from chloroform–ether. *5-Phenyl-2-phenylacetamidocarbethoxymethylthiazolidine-4-carboxylic acid hydrochloride* (X; R = CH_2Ph, R′ = Et) was a white, amorphous solid, m. p. 100° (decomp.) (Found: C, 54·9; H, 5·5; N, 6·2. $C_{25}H_{31}O_5N_2ClS,H_2O$ requires C, 54·7; H, 5·6; N, 5·8%). The free *base* was obtained with chloroform and aqueous potassium acetate as a white powder, m. p. *ca.* 130° (decomp.) (Found: C, 62·5; H, 5·9; N, 6·7. $C_{25}H_{30}O_5N_2S$ requires C, 61·7; H, 5·7; N, 6·5%). It is probably a mixture of stereoisomers.

5-Phenyl-2-hexoamidocarbethoxymethylthiazolidine-4-carboxylic acid hydrochloride (3·9 g.) was dissolved in 0·509*N*-sodium hydroxide (52·5 c.c.) and kept for 23 hours. On filtration of the solution through charcoal, addition of acetic acid (1·58 g.) and aqueous lead acetate (30%; 12 c.c.) at 0°, a white precipitate (4·2 g.) was obtained. After being thoroughly washed, dried, and suspended in ethanol (30 c.c.) it was decomposed with hydrogen sulphide for 20 minutes. The lead sulphide was washed with ethanol (3 × 5 c.c.), and the filtrate evaporated *in vacuo*. The residue was dried and triturated with ether–light petroleum (1 : 1). The solid product (2·35 g.) had m. p. 102—104° (decomp.), and separated from chloroform–light petroleum; *5-phenyl-2-hexoamidocarboxymethylthiazolidine-4-carboxylic acid* had m. p. 108° (decomp.) (Found: C, 56·6; H, 6·4; N, 6·4. $C_{18}H_{24}O_5N_2S$ requires C, 56·8; H, 6·4; N, 7·4%). The foregoing acid (22 mg.), acetic anhydride (0·2 c.c.), and pyridine (0·1 c.c.) were heated together at 50° for 15 minutes, and solvents removed at 0·1 mm. (20 minutes). The residue was dissolved in 5% phosphate buffer (10 c.c.) at pH 7·0. It was inactive, as in a blank experiment. The same result was obtained when the acid was set aside with acetic anhydride and pyridine or triethylamine for 1·5 or 22 hours, or was heated with acetic anhydride alone, or in admixture with methyl oxalate, for 3 minutes. Keeping the acid with carbon suboxide or benzoyl chloride and pyridine for 20 minutes likewise gave inactive products. β-Phenylcysteine hydrochloride (22 mg.) was kept for 14 hours with aqueous sodium acetate (50 mg./1 c.c.) and 2-benzyl-4-ethoxymethyleneoxazolone (25 mg.) in dioxan (1·0 c.c.). The mixture was diluted with 5% phosphate buffer (20 c.c.) and assayed. It was inactive. Similarly, no activity was obtained by use of phenylcysteine hydrochloride and the sodium salt of 2-benzyl-4-hydroxymethyleneoxazolone in buffer or with the ethoxymethylene-oxazolone in acetic anhydride and pyridine overnight or at 60° for 10 minutes.

(*b*) *Further Condensations with 2-Benzyl-4-ethoxymethyleneoxazolone.*—(i) *β-Phenylcysteine.* β-Phenylcysteine hydrochloride (12·7 mg.), pyridine (2·5 c.c.), and the oxazolone (25·2 mg.) were heated at 100° for 30 minutes and then at 110° with a catalytic quantity of pyridine hydrochloride for 15 minutes. Solvents were removed at 0·1 mm. pressure, and the residue dissolved in acetone (6·4 c.c.), water (3·2 c.c.), and 5% phosphate buffer (4·2 c.c.) at pH 7·0. No activity was observed. β-Phenylcysteine hydrochloride (13·2 mg.), pyridine (2·5 c.c.), and the oxazolone (30·9 mg.) were heated at 100° for 30 minutes. Treatment as above gave an inactive solution. Repetition of the above experiments, and working up the residue from removal of solvents by shaking it with ether and buffer, likewise gave no activity. The amino-mercapto-acid itself was inactive.

(ii) *β-(p-Chlorophenyl)cysteine.* The hydrochloride of the mercapto-amino-acid (4·8 mg.) and 2-benzyl-4-ethoxymethylene-5-oxazolone (11·2 mg.) were heated together in dry pyridine (2 c.c.) at 100° for 0·5 hour. Pyridine hydrochloride (0·5 mg.) was added, the solution heated at 110—115° for 15 minutes and then chilled in ice, and pyridine removed in a vacuum at room temperature. The residue was dissolved in acetone (1 c.c.) and the solution diluted to 5 c.c. bulk with 5% phosphate buffer at pH 7·0.

(iii) *β-(p-Methoxyphenyl)cysteine.* The same method was used with mercapto-amino-acid hydrochloride (5 mg.) and the oxazolone (10 mg.).

In neither case (ii) nor case (iii) was antibiotic activity observed, although blanks with the mercapto-amino-acid hydrochlorides at concentrations of 1 mg./c.c. gave 6-mm. zones of inhibition of bacteria in the plate test.

Reactions with 2-Mercapto-4-ethoxymethylenethiazolin-5-one.—Glycine ether ester hydrochloride (0·347 g.) in acetone (5 c.c.) and 1·1*N*-potassium hydroxide (2·27 c.c.) was treated with the thiazolinone (0·472 g.) in warm acetone (20 c.c.). After this had been kept for 2·5 hours at room temperature, acetone (15 c.c.) was added and the mixture set aside overnight. The product (0·2 g.), m. p. 211° (decomp.), was filtered off and a further quantity (0·32 g.) obtained from the filtrate by rubbing with ether. Recrystallised from ethanol, *2-mercapto-4-carbethoxymethylaminomethylthiazolin-5-one* (XV; R = CH_2CO_2Et) separated as yellow plates or laths, m. p. 210° (decomp.) (Found: C, 38·5; H, 4·2; N, 11·3. $C_7H_{10}O_3N_2S_2$ requires C, 39·0; H, 4·1; N, 11·4%). Light absorption (ethanol): $\lambda_{max.}$ = 2450 and 3370 A. ($E^{1\%}_{1cm.}$ 400 and 570 respectively).

Glycine (0·187 g.) in acetone (5 c.c.) and water (30 c.c.) containing 1·1*N*-potassium hydroxide (2·27 c.c.) was treated with the thiazolinone (0·47 g.) in warm acetone (20 c.c.), and the mixture shaken for 2 hours and then set aside for 26 hours. 0·945*N*-Hydrochloric acid (2·65 c.c.) was added and the solution evaporated to small bulk *in vacuo*. The crystalline deposit (0·45 g.), m. p. 225° (decomp.), was

washed with water and recrystallised from acetic acid, *2-mercapto-4-carboxymethylaminomethylenethiazolin-5-one* (XV; R = $CH_2{\cdot}CO_2H$) separating as sandy prisms, m. p. 222° (decomp.) (Found : C, 32·5; H, 3·1; N, 12·6. $C_6H_6O_3N_2S_2$ requires C, 33·0; H, 2·8; N, 12·8%). Light absorption (ethanol) : $\lambda_{max.}$ = 2470 and 3390 A. ($E^{1\%}_{1cm.}$ 450 and 590 respectively).

DL-Alanine methyl ester (0·347 g.) in acetone (5 c.c.) and 1·1N-potassium hydroxide (2·27 c.c.) was treated as above with the thiazolinone (0·47 g.) in warm acetone (20 c.c.). *2-Mercapto-4-(1'-carbomethoxypropylaminomethylene)thiazolin-5-one* (XV; R = CHMe·CO_2Me) (0·45 g.) recrystallised from ethanol as yellow prisms, m. p. 210—211° (decomp.) (Found : C, 38·9; H, 4·3; N, 11·2. $C_8H_{10}O_3N_2S_2$ requires C, 39·0; H, 4·1; N, 11·4%). Light absorption (ethanol) : $\lambda_{max.}$ = 2450, 2500, and 3640 A. ($E^{1\%}_{1cm.}$ 470, 450, and 660 respectively).

The method for glycine above was used for *S*-benzylpenicillamine (0·597 g.) in 1·1N-potassium hydroxide (2·27 c.c.) and acetone (5 c.c.) with the thiazolinone (0·472 g.) in acetone (20 c.c.). *2-Mercapto-4-(1'-carboxy-2'-benzylthio-2' : 2'-dimethylpropylaminomethyl)thiazolin-5-one* [XV; R = $Me_2C(SCH_2Ph){\cdot}CH{\cdot}CO_2H$] (0·95 g.) separated from acetone–water and acetic acid as yellow needles, m. p. 220° (decomp.) (Found : C, 50·2; H, 5·0. $C_{15}H_{18}O_3N_2S_3$ requires C, 50·2; H, 4·7%). Light absorption (ethanol) : $\lambda_{max.}$ = 2450 and 3440 A. ($E^{1\%}_{1cm.}$ 300 and 490 respectively).

The thiazolinone (1·89 g.) and toluene-α-thiol (1·24 g.) were heated at 100° for 5 minutes with triethylamine (1 c.c.). The red solution was shaken with chloroform and 2N-hydrochloric acid. The product (0·7 g.) was filtered off, and recrystallised from acetic acid and ethanol repeatedly, giving one *isomer* of *2-mercapto-4-benzylthiomethylenethiazolin-5-one* (XVI) as yellow needles, m. p. 185° (Found : C, 50·0; H, 3·3; N, 5·0; S, 35·7. $C_{11}H_9ONS_3$ requires C, 49·4; H, 3·4; N, 5·2; S, 36·0%). Light absorption (ethanol) : $\lambda_{max.}$ = 2600, 2970, and 3650 A. ($E^{1\%}_{1cm.}$ 215, 195, and 500 respectively). The filtrate was separated, and the washed chloroform solution evaporated. Treatment of the residue with ether gave a crystalline precipitate (0·8 g.). Recrystallised from acetic acid and ethanol the second *isomer* formed prisms or needles, m. p. 143° (Found : C, 49·5; H, 3·4; N, 5·2. $C_{11}H_9ONS_3$ requires C, 49·4; H, 3·4; N, 5·2%). The m. p. of this was undepressed on admixture with its isomer, and crystallisation from acetic acid caused partial conversion into the higher-melting product.

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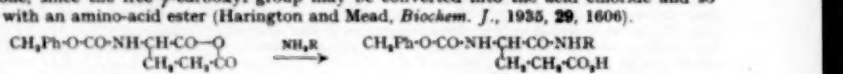
399. *Amino-acids and Peptides. Part I. An Examination of the Use of Carbobenzyloxy-L-glutamic Anhydride in the Synthesis of Glutamyl-peptides.*

By W. J. LE QUESNE and G. T. YOUNG.

In the preparation of α-L-glutamyl amides, peptides, and esters by the ring opening of *N*-carbobenzyloxy-L-glutamic anhydride, appreciable amounts of the γ-isomers may also be formed. With hydrazine, a mixture of α- and γ-acid hydrazides has been obtained. Reaction of the anhydride with the appropriate amino-acid esters yielded carbobenzyloxy-α-L-glutamyl-L-valine ethyl ester, carbobenzyloxy-α-L-glutamyl-L-leucine ethyl ester, and diethyl carbobenzyloxy-α-L-glutamyl-L-aspartate; in each case purification was effected by fractional extraction with aqueous sodium carbonate. Hydrolysis and hydrogenation then yielded the corresponding dipeptides.

After reaction of the anhydride with ethanol, this method of purification enabled crystalline α-ethyl carbobenzyloxy-L-glutamate to be isolated, which on hydrogenation gave α-ethyl L-glutamate; evidence is given that the compounds previously ascribed these structures are in fact racemic. α-Benzyl carbobenzyloxy-L-glutamate has now been obtained crystalline.

THE classical synthesis of α-glutamyl peptides depends on the reaction of *N*-carbobenzyloxy L-glutamic anhydride (I) with amino-acid esters, followed by hydrolysis and hydrogenation (Bergmann and Zervas, *Ber.*, 1932, **65**, 1192). In analogous fashion, ammonia reacts with the anhydride to give carbobenzyloxy-L-*iso*glutamine (II; R = H), which on hydrogenation yields L-*iso*glutamine. The anhydride ring may also be opened with alcohols or with alkoxides, and the α-esters so formed have been used for the synthesis of γ-glutamyl-peptides such as glutathione, since the free γ-carboxyl group may be converted into the acid chloride and so coupled with an amino-acid ester (Harington and Mead, *Biochem. J.*, 1935, **29**, 1606).



(I.) (II.)

There have, however, been indications that the anhydride ring may not always open exclusively in this direction. With glycylglycine ethyl ester, Bergman, Zervas, and Fruton

(*J. Biol. Chem.*, 1936, **115**, 606) obtained by repeated recrystallisation only a small yield of the α-derivative and concluded that a considerable portion of the γ-isomer had been formed. Melville (*Biochem. J.*, 1935, **29**, 179) examined the reaction with ammonia, and estimated that the crude L-*iso*glutamine contained some 14% of L-glutamine. More recently, Boothe *et al.* (*J. Amer. Chem. Soc.*, 1949, **71**, 2310) separated both of the possible isomers from the reaction of the anhydride with triethyl α-L-glutamyl-L-glutamate. Similar anomalies occur with the analogous carbobenzyloxy-L-aspartic anhydride; from the reaction with glycine ethyl ester the α-derivative was obtained (Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, 1935, **111**, 235), but with tyrosine ethyl ester the β-compound was isolated (Bergmann, Zervas, Salzmann, and Schleich, *Z. physiol. Chem.*, 1934, **224**, 17). Investigations in the aspartic acid series will form the subject of a later communication. Other acyl-L-glutamic anhydrides appear to react irregularly; Nicolet (*J. Amer. Chem. Soc.*, 1930, **52**, 1192) has stated that acetyl-L-glutamic anhydride yields the γ-amide with ammonia and with aniline, and King and Kidd (*J.*, 1949, 3315) have found that phthaloyl-L-glutamic anhydride also gives γ-derivatives.

It seemed possible that the ambiguity of the anhydride route might be avoided, if hydrazine were to react with carbobenzyloxy-L-glutamic anhydride to yield an acid hydrazide of determinable structure; a preliminary note of the results of this investigation has appeared (Le Quesne and Young, *Nature*, 1949, **163**, 604). With aqueous hydrazine at 0°, a crystalline hydrazide was obtained in good yield. The melting points of successive preparations were reasonably sharp but varied between 166° and 171°, being unchanged in each case by recrystallisation; the benzylidene derivatives also varied in melting point. Conversion into the azide and coupling with glycine ethyl ester gave a product from which a small quantity of carbobenzyloxy-α-L-glutamylglycine ethyl ester was isolated, but hydrolysis and hydrogenation of the coupling product gave a mixture of α- and γ-glutamyl-peptides since with ninhydrin 0·8 mole of carbon dioxide was evolved (Van Slyke, Dillon, MacFadyen, and Hamilton, *J. Biol. Chem.*, 1941, **141**, 627). Curtius degradation of the azide in benzyl alcohol gave γγ-dicarbobenzyloxyaminobutyric acid (which on hydrogenation yielded β-formylpropionic acid, identified as the *p*-nitrophenylhydrazone), but hydrogenation of the ether-soluble portion of the degradation products gave L-αγ-diaminobutyric acid, characterised as the dipicrate. It is clear therefore that the carbobenzyloxy-L-glutamylhydrazide was a mixture of the α- and the γ-isomer, which repeated crystallisation failed to separate. Authentic samples of both isomers have since been prepared (Part II; Le Quesne and Young, following paper) and from their known specific rotations it appears that the samples prepared by the anhydride route varied greatly in composition, containing between 8 and 88% of the α-form. Reaction in chloroform solution gave similar mixtures.

It seems likely that in ring openings of this type we must expect the formation of both isomers; crystallisation of the main product may thus be hindered, whilst in some cases mixed crystals may be formed. We have therefore developed a method which has proved useful for the purification of certain of such products. The acid strength of carbethoxyglycine (pK' 3·65) is considerably greater than that of acetic acid (pK 4·76) and it is therefore to be expected that coupling products with free α-carboxyl groups will be more acidic than their γ-isomers. Fractional extraction with aqueous sodium carbonate of solutions of such materials in organic solvents has in fact been found of great value. In this way it has been found possible to isolate a small sample of carbobenzyloxy-γ-L-glutamylglycine ethyl ester from the reaction of the anhydride (I) with glycine ethyl ester.

With this procedure, we have examined the reaction of carbobenzyloxy-L-glutamic anhydride with the ethyl esters of L-valine, L-leucine, and L-aspartic acid. For the coupling we have used a modification of the method of Boothe *et al.* (*loc. cit.*); the ester hydrochloride was dissolved in aqueous potassium hydrogen carbonate in contact with a layer of ethyl acetate, and the anhydride in ethyl acetate solution was added gradually with stirring. In this way we obtained carbobenzyloxy-α-L-glutamyl-L-valine ethyl ester, which on hydrolysis yielded carbobenzyloxy-α-L-glutamyl-L-valine; hydrogenation gave α-L-glutamyl-L-valine. Analogous series of reactions yielded α-L-glutamyl-L-leucine and -L-aspartic acid. Whilst exploring this method of coupling, we prepared also by this route the previously known ethyl esters of carbobenzyloxy-α-L-glutamyl-glycine, -L-glutamic acid, and -glycylglycine. The yields were somewhat lower (*ca.* 40% calculated on the anhydride) than normal, but the economy in the use of ester is considerable. In the last case the yield was only 21%, but this is perhaps to be expected since the conditions would permit some cyclisation to diketopiperazine.

For the preparation of carbobenzyloxy-L-aspartic anhydride, Miller, Behrens, and du Vigneaud (*J. Biol. Chem.*, 1941, **140**, 411) found it advantageous to close the ring by the use

of acetic anhydride at room temperature. We find that similarly mild conditions, followed by vacuum-distillation of the solvent at 50—60°, lead to carbobenzyloxy-L-glutamic anhydride of slightly increased optical activity ($[\alpha]_D$ −45·1° ± 0·2° in glacial acetic acid; Bergmann and Zervas, *loc. cit.*, reported $[\alpha]_D$ −44·1°).

We then extended our investigation of the ring opening of carbobenzyloxy-L-glutamic anhydride to the reaction with alcohols. α-Methyl carbobenzyloxy-L-glutamate has been obtained as a syrup by reaction with sodium methoxide (Harington and Mead, *loc. cit.*); with sodium ethoxide Melville (Thesis, London, 1934) obtained an oil which he considered to be α-ethyl carbobenzyloxy-L-glutamate admixed with some 30% of the γ-isomer. By treating the anhydride with ethanol at 125°, Neuberger (*Biochem. J.*, 1936, **30**, 2085) obtained a syrup which slowly crystallised, yielding a product, m. p. 100°, which appeared to be the α-ester. Since then, other workers have made unsuccessful attempts to repeat this preparation (see, *e.g.*, Boothe *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1099). Despite many variations in conditions we also failed to obtain this compound, but by fractional extraction of the reaction products with aqueous carbonate we isolated instead a substance, m. p. 46—48°, which with ammonia yielded carbobenzyloxy-L-*iso*glutamine and with hydrazine gave carbobenzyloxy-α-L-glutamylhydrazide (see Le Quesne and Young, following paper). Hydrogenation gave material, m. p. 115—117°, compared with 110° reported by Neuberger for his α-ethyl L-glutamate. It appeared possible that it was a case of polymorphism, and through the kindness of Professor A. C. Chibnall and Dr. Neuberger we obtained a small specimen of the higher-melting material prepared by Neuberger's method at Cambridge. A mixture of the two melted over a considerable range and interconversion could not be achieved. Finally, we prepared carbobenzyloxy-DL-glutamic anhydride, which in hot ethanol yielded a crystalline product shown by its properties to be α-ethyl carbobenzyloxy-DL-glutamate, m. p. 99—101°; mixed with the Cambridge sample (of m. p. 95—97°), the m. p. was 95—99°. For comparison we prepared γ-ethyl carbobenzyloxy-DL-glutamate from γ-ethyl-DL-glutamate; it had m. p. 83—85°, depressed on admixture with the isomer. The ease of crystallisation and low solubility of the racemic α-derivative would explain its isolation from syrups in which it is a minor constituent. We consider therefore the compounds reported by Neuberger to be racemic and we place on record our constants for α-ethyl carbobenzyloxy-L-glutamate and α-ethyl-L-glutamate.

α-Benzyl carbobenzyloxy-L-glutamate has previously been prepared as an oil, by treating the anhydride with benzyl alcohol at 100° (Bergmann, Zervas, and Salzmann, *Ber.*, 1933, **66**, 1288). By fractional extraction with aqueous sodium carbonate of a solution of the reaction products in ether, we have now obtained this useful intermediate as a crystalline solid, m. p. 78—81°.

Experimental.

All m. p.s are uncorrected. Combustion analyses are by Drs. Weiler and Strauss and by Mr. F. C. Hall.

Reaction between Carbobenzyloxy-L-glutamic Anhydride and Hydrazine.—(a) *In aqueous solution.* Carbobenzyloxy-L-glutamic anhydride (12 g.) was dissolved portion-wise with stirring at 0° in aqueous hydrazine hydrate (30%; 48 ml.). The solution was acidified to Congo-red with concentrated hydrochloric acid, and then saturated aqueous sodium acetate was added until it was no longer acid to Congo-red. After 30 minutes, the precipitate was filtered off and washed with water. Recrystallisation from boiling water (250 ml.) gave mixed crystals (*A*) of carbobenzyloxy-α- and -γ-L-glutamylhydrazides (11·25 g., 84%), m. p. 166—167° raised by recrystallisation to 168° (Found: C, 52·6; H, 5·7; N, 14·5. Calc. for $C_{13}H_{17}O_5N_3$: C, 52·9; H, 5·8; N, 14·2%), $[\alpha]_D^{25}$ −17·9° (*c*, 6·19 in 0·5*N*-hydrochloric acid); other samples had $[\alpha]_D$ varying between −14·2° and −22·2°.

(b) *In chloroform solution.* A solution of carbobenzyloxy-L-glutamic anhydride (5 g.) in chloroform (25 ml.) was added gradually with shaking to a mixture of hydrazine (anhydrous; 1·7 ml.) and chloroform (25 ml.) at 0°. After some minutes, the solution was extracted with water (10 ml.) twice and the combined aqueous extracts were washed with ether. The aqueous layer was acidified to Congo-red with concentrated hydrochloric acid, filtered, and neutralised with saturated aqueous sodium acetate. It was set aside at 0° for 30 minutes and the mixed crystals were filtered off (2·85 g., 64%), m. p. 154—158°, raised by recrystallisation to 163—166°, $[\alpha]_D^{25}$ −19·0° (*c*, 7·9 in 0·5*N*-hydrochloric acid).

Benzylidene Derivative of Product A.—Carbobenzyloxy-L-glutamylhydrazide (*A*) (0·1 g.) was dissolved in aqueous acetic acid (50%; 10 ml.), and benzaldehyde (0·1 ml.) added. After 30 minutes at 0°, the precipitate was filtered off, washed with water and ether, and air-dried; it had m. p. 197°, unaltered by recrystallisation from aqueous ethanol (Found: C, 62·8; H, 5·6; N, 11·1. Calc. for $C_{20}H_{21}O_5N_3$: C, 62·6; H, 5·5; N, 11·0%). Different samples of hydrazide gave products melting between 179° and 203°.

Conversion of Product A into the Azide, and Coupling with Glycine Ethyl Ester.—A solution of carbobenzyloxy-L-glutamylhydrazide (*A*) (2·8 g.) in a mixture of water (60 ml.) and concentrated hydrochloric acid (3·5 ml.) was covered with chloroform (30 ml.) and stirred mechanically at 0°. A solution of sodium nitrite (1·1 g.) in water (5 ml.) was added portion-wise during 5 minutes and stirring continued for an additional 10 minutes. The chloroform layer was then separated, washed twice with ice-cold water, and dried (Na_2SO_4) for a few seconds. It was then slowly added at 0° to a solution of glycine

ethyl ester (from 12 g. of hydrochloride) in chloroform (75 ml.) and left for 30 minutes in the ice-bath. After 5 hours at room temperature it was washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated under reduced pressure. The product (*B*) (2·05 g., 59%) crystallised under light petroleum; it had m. p. 80—90°, raised by repeated recrystallisation from ethyl acetate–light petroleum to 96—104°.

To the solution obtained by extraction of part of this material with boiling ether, light petroleum was added. After the mixture had been kept at 0° overnight, a little carbobenzyloxy-α-L-glutamylglycine ethyl ester was filtered off; it had m. p. 120—123°, and mixed with the ring-opening product had m. p. 119—121°.

L-Glutamylglycine from Coupling Product B.—Carbobenzyloxy-L-glutamylglycine ethyl ester (mixture of α- and γ-compounds, Product *B* above) (0·45 g.) was dissolved in N-potassium hydroxide (2·5 ml.) and left for 30 minutes at room temperature. The solution was then acidified with 5N-hydrochloric acid and extracted twice with ethyl acetate; the combined extracts were washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated under reduced pressure. The remaining oil was dissolved in aqueous methanol and hydrogenated in the presence of palladium black at atmospheric pressure. The filtrate obtained was evaporated to small volume under diminished pressure and excess of ethanol added. The L-glutamylglycine obtained by filtration gave 0·8 mole of carbon dioxide with ninhydrin at 100° and pH 2·5.

Curtius Degradation of Product A.—A solution of carbobenzyloxy-L-glutamylhydrazide (A) (2 g.) in a mixture of water (50 ml.) and concentrated hydrochloric acid (2·5 ml.) was covered with a layer of ether (50 ml.). With mechanical stirring at 0°, an aqueous solution of sodium nitrite (0·8 g.) was added portion-wise during 5 minutes, then stirring continued for another 10 minutes. The ethereal layer was washed twice with ice-cold water, dried (Na_2SO_4) for a few minutes at 0°, and filtered into redistilled benzyl alcohol (6 ml.). The ether was removed under reduced pressure at room temperature, then the solution slowly heated to 100° and kept at that temperature for 2 hours. After cooling, ether (20 ml.) and light petroleum (b. p. 60—80°; 100 ml.) were added. The oil which separated was triturated with ether, a white solid remaining; the ethereal extract, evaporated *in vacuo*, gave an oil (*C*). The solid *γγ-dicarbobenzyloxyaminobutyric acid* (0·3 g., 12%) had m. p. 168—171°, raised by recrystallisation from aqueous ethanol to 173—174° (Found: C, 62·3; H, 5·5; N, 7·2. $C_{20}H_{22}O_8N_2$ requires C, 62·2; H, 5·7; N, 7·3%).

β-Formylpropionic Acid.—A solution of *γγ*-dicarbobenzyloxyaminobutyric acid in aqueous methanol containing a drop of acetic acid and some palladium black was hydrogenated at normal pressure. The solution obtained after filtration reduced Fehling's solution and ammoniacal silver nitrate. The methanol was removed under reduced pressure and the remaining solution treated with *p*-nitrophenylhydrazine in dilute hydrochloric acid, giving a yellow precipitate. This was recrystallised from hot water giving golden plates of the *β*-formylpropionic acid *p*-nitrophenylhydrazone, m. p. 174—177° (Found: C, 50·9; H, 4·7; N, 17·9. Calc. for $C_{10}H_{11}O_4N_3$: C, 50·6; H, 4·7; N, 17·7%).

L-αγ-Diaminobutyric Acid.—The ether-soluble oil (*C*) from the Curtius degradation was hydrogenated in aqueous methanol acidified with acetic acid, palladium black being used as catalyst. The solution was filtered and evaporated to small volume under reduced pressure. Saturated aqueous picric acid (40 ml.) was added, and the solution left at 0° overnight. Yellow crystals of the dipricrate of L-αγ-diaminobutyric acid were obtained, having m. p. 180—182° (Found: C, 33·1; H, 3·1; N, 19·3. Calc. for $C_{16}H_{16}O_{18}N_8$: C, 33·3; H, 2·8; N, 19·5%).

Carbobenzyloxy-L-glutamic Anhydride.—Carbobenzyloxy-L-glutamic acid (20 g.) and acetic anhydride (50 ml.) were set aside with occasional shaking until complete dissolution occurred. The solvent was removed *in vacuo* at 50—60° and the residue dissolved in dry chloroform (40 ml.) and ether (40 ml.) by warming. After 1 hour at 0°, the carbobenzyloxy-L-glutamic anhydride was filtered off (13·0 g., 70%), m. p. 93—94°, $[\alpha]_D$ −45·1° (*c*, 9·98 in glacial acetic acid).

L-Valine Ethyl Ester Hydrochloride.—L-Valine (2 g.) and ethanol (25 ml.) saturated with hydrogen chloride were refluxed together for 3 hours. After removal of the solvent under reduced pressure, the *ester hydrochloride* crystallised when kept in a vacuum-desiccator; recrystallisation from ethyl acetate–light petroleum gave deliquescent crystals (2·2 g., 71%), m. p. 93—97° in a sealed tube (Found: Cl, 19·9. $C_7H_{16}O_2NCl$ requires Cl, 19·8%).

Carbobenzyloxy-α-L-glutamyl-L-valine Ethyl Ester.—A solution of L-valine ethyl ester hydrochloride (1·1 g.) and potassium hydrogen carbonate (1·5 g.) in water (10 ml.), covered with ethyl acetate (10 ml.), was stirred mechanically while a solution of carbobenzyloxy-L-glutamic anhydride (1·5 g.) in ethyl acetate (10 ml.) was added portion-wise during 2—3 minutes; stirring was continued for 2 hours. Next morning the aqueous layer was separated, acidified with 5N-hydrochloric acid and extracted twice with ethyl acetate. After being washed with water, the ethyl acetate layer was successively extracted with aqueous sodium carbonate (four portions each containing 0·06 g., then 0·5 g.) and the separate extracts acidified with 5N-hydrochloric acid. The oil which separated from the last fraction soon crystallised, and repetition of the fractional extraction procedure on the oil obtained from the penultimate extraction gave more solid material. Recrystallisation from ethyl acetate gave *carbobenzyloxy-α-L-glutamyl-L-valine ethyl ester* (1·0 g., 32%), m. p. 119—121°, raised to 122—124° by further recrystallisation (Found: N, 7·0. $C_{20}H_{30}O_7N_2$ requires N, 6·9%).

Carbobenzyloxy-α-L-glutamyl-L-valine.—Carbobenzyloxy-α-L-glutamyl-L-valine ethyl ester (0·8 g.) in N-sodium hydroxide (5 ml.) was left for 1 hour at room temperature. Acidification with 5N-hydrochloric acid gave an oil which soon crystallised. After 30 minutes, the *carbobenzyloxy-α-L-glutamyl-L-valine* was filtered off, washed with water, air-dried, and washed with boiling ether. The product (0·5 g., 68%) had m. p. 130—132°, raised to 131—133° by recrystallisation from ethyl acetate–light petroleum (Found: C, 56·8; H, 6·4; N, 7·8. $C_{18}H_{26}O_7N_2$ requires C, 56·8; H, 6·4; N, 7·4%).

α-L-Glutamyl-L-valine.—Carbobenzyloxy-α-L-glutamyl-L-valine (0·7 g.) was hydrogenated in the usual way in aqueous methanol. *α-L-Glutamyl-L-valine* separated during the reduction and, after filtration, was extracted with boiling water and reprecipitated with ethanol as shiny plates (0·45 g.), m. p. 182—183°, raised by recrystallisation from aqueous ethanol to 189—190° (Found: C, 49·9; H,

7·4; N, 10·8. $C_{16}H_{19}O_5N_3$ requires C, 48·8; H, 7·4; N, 11·4%), $[\alpha]_D^{25}$ +24·5° (*c*, 2·65 in water containing 1 mole of hydrochloric acid).

Carbobenzyloxy-α-L-glutamyl-L-leucine Ethyl Ester.—A solution of L-leucine ethyl ester hydrochloride (1·25 g.; m. p. 127—129°; from commercial L-leucine) and potassium hydrogen carbonate (2 g.) in water (15 ml.), covered with ethyl acetate (10 ml.), was treated with carbobenzyloxy-L-glutamic anhydride (1·65 g.) in ethyl acetate (10 ml.) as for the valine ester. The final fraction from the sodium carbonate treatment was extracted into ethyl acetate, dried (Na_2SO_4), and evaporated under reduced pressure. The product slowly crystallised under light petroleum, and was recrystallised from toluene (3—4 ml.), giving *carbobenzyloxy-α-L-glutamyl-L-leucine ethyl ester* (0·8 g., 30%), m. p. 88—94°, raised to 94—96° by recrystallisation from ethyl acetate–light petroleum (Found: C, 59·5; H, 7·0; N, 6·8. $C_{21}H_{30}O_7N_2$ requires C, 59·7; H, 7·2; N, 6·6%).

α-L-Glutamyl-L-leucine.—Carbobenzyloxy-α-L-glutamyl-L-leucine ethyl ester (0·7 g.) was dissolved in N-sodium hydroxide (5·5 ml.) and left at room temperature for 1 hour. The solution was acidified with 5N-hydrochloric acid and extracted 3 times with ethyl acetate. The combined extracts were washed with a little water, dried (Na_2SO_4), and evaporated under reduced pressure, leaving carbobenzyloxy-α-L-glutamyl-L-leucine as a syrup. This was hydrogenated in the usual way in methanolic solution. Reduction took about 12 hours. The solution was filtered and the precipitate washed with boiling water. The combined filtrates were evaporated under reduced pressure to small volume, and ethanol was added. After 1 hour at 0°, the *α-L-glutamyl-L-leucine* was filtered off and washed with ethanol. It forms shiny plates, m. p. 196—197° (Found: C, 50·8; H, 7·5; N, 10·8. $C_{11}H_{20}O_5N_2$ requires C, 50·7; H, 7·7; N, 10·8%), $[\alpha]_D^{25}$ +8·6° (*c*, 1·75 in water containing 1 mole of hydrochloric acid).

Diethyl Carbobenzyloxy-α-L-glutamyl-L-aspartate.—Diethyl L-aspartate hydrochloride (3·6 g.; recrystallised from ethanol–ether; m. p. 98—102° in a sealed tube) and potassium hydrogen carbonate (4·0 g.) were dissolved in water (40 ml.), and ethyl acetate was added (20 ml.). The mixture was treated with a solution of carbobenzyloxy-L-glutamic anhydride (3·6 g.) in ethyl acetate (20 ml.) as for the valine ester. The last fraction and that obtained by refractionation of previous fractions with sodium carbonate gave, on acidification, oils which rapidly crystallised to give *diethyl carbobenzyloxy-α-L-glutamyl-L-aspartate* (2·6 g., 43%), m. p. 107—118°, raised to 118—120° by recrystallisation from ethyl acetate–light petroleum (Found: C, 55·6; H, 6·3; N, 6·0. $C_{21}H_{28}O_9N_2$ requires C, 55·8; H, 6·2; N, 6·2%).

Carbobenzyloxy-α-L-glutamyl-L-aspartic Acid.—Diethyl carbobenzyloxy-α-L-glutamyl-L-aspartate (1·5 g.) was dissolved in N-sodium hydroxide (11 ml.) and left at room temperature for 40 minutes. After being acidified with 5N-hydrochloric acid and kept for 30 minutes, *carbobenzyloxy-α-L-glutamyl-L-aspartic acid* (1·1 g., 79%) was filtered off, washed with a little water, and dried. The m. p. was 170—173°, raised by recrystallisation from hot water to 171—174° (Found: C, 51·2; H, 5·2; N, 6·8. $C_{17}H_{20}O_9N_2$ requires C, 51·5; H, 5·1; N, 7·1%).

α-L-Glutamyl-L-aspartic Acid.—Carbobenzyloxy-α-L-glutamyl-L-aspartic acid was hydrogenated in the usual manner in aqueous methanol. Evaporation of the filtrate and washings to small volume, and precipitation with ethanol, gave *α-L-glutamyl-L-aspartic acid monohydrate*, m. p. 138—141° (Found: C, 38·6; H, 5·7; N, 9·9. $C_9H_{14}O_7N_2.H_2O$ requires C, 38·6; H, 5·8; N, 10·0%), $[\alpha]_D^{25}$ +30·2° (*c*, 2·32 in water).

Diethyl Carbobenzyloxy-α-L-glutamyl-L-glutamate.—Diethyl L-glutamate hydrochloride (3 g.) was dissolved in aqueous potassium hydrogen carbonate covered with ethyl acetate, and treated with carbobenzyloxy-L-glutamic anhydride (3 g.) in a similar manner to the above esters. Diethyl carbobenzyloxy-α-L-glutamyl-L-glutamate was obtained (2·3 g., 43%), m. p. 132—134°.

Carbobenzyloxy-α- and -γ-glutamylglycine Ethyl Esters.—Glycine ethyl ester hydrochloride (2·0 g.) was treated similarly with potassium hydrogen carbonate and carbobenzyloxy-L-glutamic anhydride (3·0 g.). Carbobenzyloxy-α-L-glutamylglycine ethyl ester (1·6 g., 38%), m. p. 120—123°, was obtained from the final sodium carbonate extract. Refractionation of the first extract gave a small quantity of *carbobenzyloxy-γ-L-glutamylglycine ethyl ester*, m. p. 105—108°, unchanged by admixture with the γ-compound prepared as in the subsequent paper.

Carbobenzyloxy-α-L-glutamylglycylglycine Ethyl Ester.—Glycylglycine ethyl ester hydrochloride (1·5 g.) in aqueous potassium hydrogen carbonate covered with ethyl acetate was treated with carbobenzyloxy-L-glutamic anhydride (1·8 g.) in ethyl acetate as above. From the last fractions obtained by sodium carbonate extraction, carbobenzyloxy-α-L-glutamylglycylglycine ethyl ester was isolated (0·5 g., 21%), m. p. 134—136°.

α-L-Glutamylglycylglycine.—Carbobenzyloxy-α-L-glutamylglycylglycine was hydrogenated in the usual manner in aqueous methanol. Evaporation of the filtrate to low bulk and addition of ethanol gave *α-L-glutamylglycylglycine*, m. p. 160—162° (Found: C, 41·1; H, 5·5. $C_9H_{15}O_6N_3$ requires C, 41·4; H, 5·8%).

Paper Partition Chromatography of Some α-Glutamyl-peptides.—By use of phenol saturated with water in an atmosphere containing ammonia, the following R_F values were obtained, each peptide giving a single spot with ninhydrin: α-L-glutamyl- 0·15, -L-tyrosine 0·36, -L-valine 0·42, -L-leucine 0·59, -L-glutamic acid 0·06, -L-aspartic acid 0·04, and -glycylglycine 0·19 (glycine, 0·43; glutamic acid, 0·18).

α-Ethyl Carbobenzyloxy-L-glutamate.—Carbobenzyloxy-L-glutamic anhydride (14 g.) was heated in a sealed tube with ethanol (70 ml.) at 120—130° for 4 hours. After cooling, the excess of ethanol was removed under reduced pressure, and the residue dissolved in ether. The solution was extracted with 4 successive portions of aqueous sodium carbonate (each containing 0·6 g.), then with excess. The final fraction on acidification gave an oil which rapidly solidified. Refractionation of the other extracts gave more *α-ethyl carbobenzyloxy-L-glutamate monohydrate* (total: 5·1 g., 29%), m. p. 46—48° (Found: C, 55·4; H, 6·8. $C_{14}H_{19}O_6N.H_2O$ requires C, 55·0; H, 6·5%). Drying over phosphoric oxide in a vacuum-desiccator gave the anhydrous *ester*, m. p. 46—48° (Found: C, 58·6; H, 6·3; N, 4·7. $C_{14}H_{19}O_6N$ requires C, 58·2; H, 6·2; N, 4·5%), $[\alpha]_D^{25}$ −21·4° (*c*, 7·7 in ethanol). The mixed m. p. with Prof. Chibnall's sample (m. p. 95—97°) was 41—90°.

Refractionation of the first sodium carbonate extracts gave γ-ethyl carbobenzyloxy-D-glutamate,

which after recrystallisation from ethyl acetate–light petroleum, had m. p. 82—84°. The mixed m. p. with the authentic γ-compound was 81—84°.

*Carbobenzyloxy-*DL*-glutamic Anhydride.*—Carbobenzyloxy-DL-glutamic acid (6·5 g.; m. p. 122—124°) was treated as the L-compound above, giving *carbobenzyloxy-*DL*-glutamic anhydride* (5·6 g., 90%), m. p. 108—109° (Found: C, 59·2; H, 5·2; N, 5·5. $C_{13}H_{13}O_5N$ requires C, 59·3; H, 5·0; N, 5·3%).

*α-Ethyl Carbobenzyloxy-*DL*-glutamate.*—Carbobenzyloxy-DL-glutamic anhydride (2 g.) was treated as for the L-compound. The final fractions from sodium carbonate extraction on acidification gave oils which rapidly solidified. The *α-ethyl carbobenzyloxy-*DL*-glutamate* was washed with boiling ether, and another crop was obtained by cooling the filtrate (total: 0·85 g., 35%). The m. p. was 99—101° (Found: C, 58·1; H, 6·2. $C_{14}H_{17}O_6N$ requires C, 58·2; H, 6·2%). The mixed m. p. with Prof. Chibnall's sample (m. p. 95—97°) was 95—99°.

*γ-Ethyl Carbobenzyloxy-*DL*-glutamate.*—γ-Ethyl DL-glutamate (1·6 g.) was treated in the same manner as the L-compound (Abderhalden and Nienburg, *Z. physiol. Chem.*, 1933, **219**, 155), giving *γ-ethyl carbobenzyloxy-*DL*-glutamate* (1·8 g., 64%), m. p. 82—85°, raised by recrystallisation from ether–light petroleum to 83—85°(Found: C, 58·6; H, 5·9. $C_{14}H_{17}O_6N$ requires C, 58·2; H, 6·2%). The mixed m. p. with the α-compound was 70—77°.

α-Ethyl L*-Glutamate.*—α-Ethyl carbobenzyloxy-L-glutamate was hydrogenated in the usual manner in ethanolic solution. The filtrate was evaporated to small volume and ether added. The α-ethyl L-glutamate was filtered off and reprecipitated from ethanolic solution with ether, then having m. p. 116—118°. Drying over phosphoric oxide in a vacuum-desiccator at room temperature did not remove all the solvent; heating to 100° caused decomposition.

*Carbobenzyloxy-*L*-iso*L*-glutamine.*—α-Ethyl carbobenzyloxy-L-glutamate (1 g.) was dissolved in aqueous ammonia (*d* 0·880; 10 ml.) and left for 4 days. The solution was acidified with concentrated hydrochloric acid, with cooling, and filtered after 1 hour. The carbobenzyloxy-L-*iso*glutamine was recrystallised from hot water, with m. p. 168—172° (0·7 g., 75%). The mixed m. p. with a sample prepared by Bergmann's method was 167—172°.

*α-Benzyl Carbobenzyloxy-*L*-glutamate.*—Carbobenzyloxy-L-glutamic anhydride (3 g.) and benzyl alcohol (1·5 g.) were heated at 100° for 3½ hours, cooled, and dissolved in ether. The solution was fractionally extracted with aqueous sodium carbonate. The last fraction was acidified and extracted with ether. After the ethereal layer had been dried and the solvent removed under reduced pressure, the product solidified during some days. It was washed with cold toluene (2—3 ml.) and the α-benzyl carbobenzyloxy-L-glutamate filtered off (0·8 g., 18%), having m. p. 75—80°. It was dissolved in a little ethanol, precipitated by adding water, and filtered off after being kept overnight. It was air-dried and washed with a little cold toluene, to give m. p. 78—81° (Found: C, 64·5; H, 5·6; N, 4·0. Calc. for $C_{19}H_{21}O_6N$: C, 64·8; H, 5·7; N, 3·8%).

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400. *Amino-acids and Peptides. Part II. Synthesis of α- and γ-*L*-Glutamyl-peptides by the Azide Route.*

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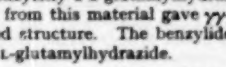
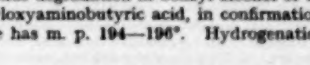
Carbobenzyloxy-α-L-glutamylhydrazide has been synthesised and its usefulness in preparing α-glutamyl-peptides examined. In general, the yields are somewhat lower than those obtained by the alternative anhydride route (preceding paper). Carbobenzyloxy-γ-L-glutamylhydrazide has been prepared in improved yield and purity and has been used for the synthesis of the following new peptides: γ-L-glutamyl-glycine, -L-glutamic acid, -L-aspartic acid, -L-tyrosine, and -glycylglycine. Preliminary results are reported of an investigation of the autohydrolysis of some α- and γ-glutamyl-peptides; there are indications that hydrolysis under these conditions may be preceded or accompanied by cyclisation to form pyrrolidone derivatives.

THE α- and γ-hydrazides of carbobenzyloxy-L-glutamic acid should clearly provide unambiguous paths for the synthesis of α- and γ-L-glutamyl-peptides. In Part I (preceding paper) it was shown that the action of hydrazine on carbobenzyloxy-L-glutamic anhydride gives a mixture of α- and γ-isomers, which cannot be separated by crystallisation. The hydrazides have therefore been prepared by other routes, and characterised, and their use in synthesis has been examined.

α-Ethyl carbobenzyloxy-L-glutamate (*loc. cit.*) with hydrazine at room temperature afforded carbobenzyloxy-α-L-glutamylhydrazide (I). Curtius degradation in benzyl alcohol of the azide formed from this material gave γγ-dicarbobenzyloxyaminobutyric acid, in confirmation of the expected structure. The benzylidene derivative has m. p. 194—196°. Hydrogenation of (I) gave α-L-glutamylhydrazide.



(I.)



(II.)

The azide prepared from (I) was coupled with glycine ethyl ester in chloroform, yielding carbobenzyloxy-α-L-glutamylglycine ethyl ester. Coupling with diethyl L-glutamate and with L-tyrosine ethyl ester gave analogous derivatives, identical with those prepared by the anhydride route, but the yields in each case were lower.

For the preparation of carbobenzyloxy-γ-L-glutamylhydrazide (II), we treated with hydrazine Abderhalden and Nienburg's γ-ethyl carbobenzyloxy-L-glutamate (*Z. physiol. Chem.*, 1933, **219**, 155), the structure of which was proved by Bergmann and Zervas (*ibid.*, 1933, **221**, 51) and by Nienburg (*Ber.*, 1935, **68**, 2232). A preliminary report of this part of our work was presented in *Nature* (1949, **163**, 604). Hegedüs had meanwhile reported (*Helv. Chim. Acta*, 1948, **31**, 737) the synthesis of this hydrazide, m. p. 170—172°, by a similar route and in 44% yield. We obtained however an 80% yield of recrystallised product of m. p. 178—179°. The benzylidene derivative has m. p. 201—202°, depressed by admixture with that of the α-hydrazide. Curtius degradation in benzyl alcohol of the azide formed from (II) gave a product which, on hydrogenation and short acid hydrolysis, yielded L-αγ-diaminobutyric acid, isolated as the dipicrate. Examination of the solution obtained after hydrogenation failed to detect the presence of the aldehyde which would result from contamination of the original material by α-hydrazide.

The usefulness of carbobenzyloxy-γ-L-glutamylhydrazide has been shown by Hegedüs (*loc. cit.*) in a novel synthesis of glutathione. We have coupled the azide with the glycine ethyl ester in chloroform, obtaining carbobenzyloxy-γ-L-glutamylglycine ethyl ester, which on saponification gave carbobenzyloxy-γ-L-glutamylglycine; hydrogenation then yielded γ-L-glutamylglycine. The presence of a free α-amino-acid group in this dipeptide was shown by the reaction with ninhydrin under standard conditions (Van Slyke, Dillon, McFadyen, and Hamilton, *J. Biol. Chem.*, 1941, **141**, 627), which gave 1·0 mole of carbon dioxide. Through analogous intermediates γ-L-glutamyl-L-glutamic acid, -L-aspartic acid, -L-tyrosine, and -glycylglycine have been synthesised.

We have successfully used the method of Boothe *et al.* (*J. Amer. Chem. Soc.*, 1949, **71**, 2304), coupling the azide with glycine in aqueous potassium hydrogen carbonate solution. With other amino-acids, we have experienced greater difficulty in obtaining pure products than when using anhydrous conditions. In general, γ-glutamyl derivatives show considerable reluctance to crystallise; this factor facilitates the isolation of α-glutamyl derivatives from mixed coupling products, but renders work upon the γ-isomers difficult.

An investigation of the autohydrolysis of α- and γ-glutamyl-peptides is now in progress and some preliminary results are of interest. Aqueous solutions of the peptides were heated at 100° and samples were examined by paper partition chromatography at various times. After 24 hours, little of the original peptide remained from γ-L-glutamyl-glycine, -L-tyrosine, -L-aspartic acid, -L-glutamic acid, or -glycylglycine; in each case, strong colours were formed with ninhydrin corresponding in position to the second-named amino-acid, the tripeptide yielding mainly glycylglycine but also some glycine. Only from the hydrolysis of γ-L-glutamyl-L-glutamic acid could a significant amount of glutamic acid be detected. From α-L-glutamylglycine and α-L-glutamyl-L-aspartic acid only small amounts of dipeptide remained after 24 hours; glycine and aspartic acid respectively were readily detected but again no glutamic acid appeared. Solutions of α-L-glutamyl-L-valine, -L-leucine, -L-tyrosine, and -L-glutamic acid showed after 24 hours not more than traces of any material giving a colour with ninhydrin. In a control experiment, after being heated for 24 hours at 100° an aqueous solution of L-glutamic acid still gave a normal though somewhat weaker chromatogram.

A possible explanation of these results is that autohydrolysis of α- and γ-glutamyl peptides is preceded or accompanied by cyclisation to form pyrrolidone derivatives, which do not give a ninhydrin reaction. In 0·5N-hydrochloric acid, where cyclisation is not to be expected, all the glutamyl-peptides examined gave chromatograms consistent with the presence of the normal hydrolysis products, including glutamic acid. These investigations are being continued.

Experimental.

All m. p.s are uncorrected. Combustion analyses are by Drs. Weiler and Strauss and by Mr. F. C. Hall.

Carbobenzyloxy-α-L-glutamylhydrazide.—α-Ethyl carbobenzyloxy-L-glutamate (2 g.; see preceding paper) in ethanol (3 ml.) was added drop-wise, with shaking, to hydrazine hydrate (3 ml.; 90%) during 5—10 minutes. After 2 days at room temperature, water (12 ml.) was added, followed by concentrated hydrochloric acid until the solution was acid to Congo-red. The solution was neutralised to Congo-red with saturated aqueous sodium acetate and left at 0° for 1 hour, and the *carbobenzyloxy-α-L-glutamylhydrazide* (1·5 g., 78%) filtered off and washed with water. The m. p. was 163—166°, raised by recrystallisation from boiling water to 168—170° (Found: C, 52·6; H, 5·7. $C_{13}H_{17}O_5N_3$ requires C, 52·9; H,

5·8%). $[\alpha]_D^{18}$ −23·4° (*c*, 8·66 in 0·5*N*-hydrochloric acid). The *benzylidene* derivative had m. p. 194—196° (Found: C, 62·2; H, 5·7; N, 11·0. $C_{20}H_{21}O_5N_3$ requires C, 62·6; H, 5·5; N, 11·0%).

Curtius Degradation of Carbobenzyloxy-α-L-glutamylhydrazide (0·5 g.) was converted into the azide in ether (20 ml.); after being dried (Na_2SO_4), the solution was added to benzyl alcohol (1·5 ml.). The ether was removed under reduced pressure and the remaining solution left overnight at room temperature, then heated at 100° for 2 hours. Ether (10 ml.) was added, and the γγ-dicarbobenzyloxyaminobutyric acid (0·3 g., 46%) filtered off. After recrystallisation from ethanol, it had m. p. 169—171°, unaltered by admixture with the product described in Part I.

α-L-Glutamylhydrazide.—Carbobenzyloxy-α-L-glutamylhydrazide in aqueous methanol was hydrogenated in the usual manner with palladium black as catalyst. The filtrate was evaporated to dryness under reduced pressure and the remaining oil triturated with ethanol, the *α-L-glutamylhydrazide* solidifying; it had m. p. 165—168°, raised by recrystallisation from aqueous ethanol to 169—171° (Found: C, 36·8; H, 6·6. $C_5H_{11}O_3N_3$ requires C, 37·2; H, 6·9%).

Carbobenzyloxy-α-L-glutamylglycine Ethyl Ester from the α-Hydrazide.—Carbobenzyloxy-α-L-glutamylhydrazide (0·85 g.) was converted into the azide in chloroform (15 ml.) in the normal manner. After being washed with water and dried (Na_2SO_4) for a few seconds, it was added at 0° portion-wise, with shaking, to a solution of glycine ethyl ester (from 3 g. of hydrochloride) in chloroform (15 ml.). The mixture was left for ½ hour at 0° and overnight at room temperature. It was then washed with 2*N*-hydrochloric acid and water, dried (Na_2SO_4), and evaporated under reduced pressure. The product solidified under light petroleum and was recrystallised from ethyl acetate–light petroleum, giving carbobenzyloxy-α-L-glutamylglycine ethyl ester (0·25 g., 24%); it had m. p. 120—122°, unchanged by admixture with the compound prepared by the anhydride ring-opening.

Diethyl Carbobenzyloxy-α-L-glutamyl-L-glutamate from the α-Hydrazide.—Carbobenzyloxy-α-L-glutamylhydrazide (0·79 g.) was converted into the azide in chloroform and added to diethyl L-glutamate (from 3·5 g. of hydrochloride) in chloroform. After 2 days at 0—5°, the solution was washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated under reduced pressure. The product was crystallised from ethyl acetate–light petroleum, giving diethyl carbobenzyloxy-α-L-glutamyl-L-glutamate (0·3 g., 24%), m. p. 131—134°, raised to 134—136° by recrystallisation. Mixed with the compound from the anhydride ring-opening, it had m. p. 133—135°.

Carbobenzyloxy-γ-L-glutamyl-L-tyrosine Ethyl Ester from the α-Hydrazide.—Carbobenzyloxy-α-L-glutamylhydrazide (1 g.) was converted into the azide in chloroform solution and added to L-tyrosine ethyl ester (2·8 g.) in chloroform (15 ml.). The solution was left for ½ hour at 0° and overnight at room temperature, washed with dilute hydrochloric acid and water, dried, and evaporated under reduced pressure. Treatment of the resultant syrup with ethanol–ether gave carbobenzyloxy-α-L-glutamyl-L-tyrosine ethyl ester (0·2 g., 12%), m. p. 162—172°, raised to 172—176° by recrystallisation from ethanol–ether. The latter value was unaltered by admixture with the product from the anhydride ring-opening.

γ-Ethyl Carbobenzyloxy-L-glutamate.—γ-Ethyl carbobenzyloxy-L-glutamate was prepared as described by Abderhalden and Nienburg (*Z. physiol. Chem.*, 1933, **219**, 155) and, recrystallised from carbon tetrachloride, had m. p. 84—86°.

Carbobenzyloxy-γ-L-Glutamylhydrazide.—γ-Ethyl carbobenzyloxy-L-glutamate (3·4 g.) in ethanol (8 ml.) was added drop-wise during 5—10 minutes to hydrazine hydrate (3·5 ml.; 100%) and left for 48 hours at room temperature. Most of the ethanol was removed under reduced pressure and after addition of water the solution was acidified to Congo-red with hydrochloric acid. It was then neutralised with saturated aqueous sodium acetate; after 1 hour at 0°, the carbobenzyloxy-γ-L-glutamylhydrazide (3·2 g., 98%) was filtered off. It had m. p. 173—174°, raised by recrystallisation from boiling water to 178—179° (2·55 g., 80%) (Found: C, 52·7; H, 5·9; N, 14·0. Calc. for $C_{13}H_{17}O_5N_3$: C, 52·9; H, 5·8; N, 14·2%). $[\alpha]_D^{18}$ −13·4° (*c*, 6·4 in 0·5*N*-hydrochloric acid). $[\alpha]_D^{18}$ −5·1° (*c*, 10·0 in water containing 1 mole of sodium hydroxide). The *benzylidene* derivative had m. p. 200—201°, depressed to 181—186° by admixture with the α-analogue (Found: C, 62·5; H, 5·7; N, 11·2. $C_{20}H_{21}O_5N_3$ requires C, 62·6; H, 5·5; N, 11·0%).

Curtius Degradation of Carbobenzyloxy-γ-L-Glutamylhydrazide.—Carbobenzyloxy-γ-L-glutamylhydrazide (0·5 g.) was converted into the azide in the usual manner, and the dried ethereal solution added to benzyl alcohol (1·5 ml.). After removal of the ether under reduced pressure, the solution was heated at 100° for 2 hours, leaving an oil completely soluble in ether. A solution of it in aqueous methanol containing a little acetic acid was hydrogenated in the usual way. The filtrate was concentrated under reduced pressure to 2 ml., concentrated hydrochloric acid (2 ml.) added, and the mixture refluxed for 75 minutes. The solution was then evaporated to dryness under diminished pressure; the residue was dissolved in a little water, and saturated aqueous picric acid (40 ml.) added. After 2 days at 0°, the dipicrate of L-αγ-diaminobutyric acid (0·1 g.) was filtered off, having m. p. 177—179°, unchanged by recrystallisation from hot water.

The solution obtained by hydrogenation did not reduce Fehling's solution or give a precipitate with *p*-nitrophenylhydrazine in dilute hydrochloric acid.

Carbobenzyloxy-γ-L-glutamylglycine Ethyl Ester.—Carbobenzyloxy-γ-L-glutamylhydrazide (2 g.) was converted into the azide in chloroform solution and added to glycine ethyl ester (from 7·5 g. of hydrochloride) in chloroform. The solution was treated in the same manner as that from the α-compound and yielded, after removal of the solvent under reduced pressure, an oil which solidified after some hours under light petroleum. *Carbobenzyloxy-γ-L-glutamylglycine ethyl ester* (1·25 g.; 50%) had m. p. 97—104°, raised to 107—109° by recrystallisation from ethyl acetate–light petroleum (Found: C, 55·7; H, 5·9. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·1%). The mixed m. p. with the α-analogue was 97—100°.

Carbobenzyloxy-γ-L-glutamylglycine.—Carbobenzyloxy-γ-L-glutamylglycine ethyl ester (1·5 g.) was dissolved in *N*-potassium hydroxide (10 ml.) and left for 2 hours at room temperature. The solution was acidified with 5*N*-hydrochloric acid and extracted with 4 successive portions (each 20 ml.) of ethyl acetate. The combined extracts were washed with small quantities of dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated under reduced pressure. The remaining *carbobenzyloxy-α-L-glutamylglycine* (0·7 g., 51%) was washed on to the filter with a little ethyl acetate. It had m. p. 159—161°, unchanged

by recrystallisation from ethyl acetate–ethanol–light petroleum (Found: C, 53·5; H, 5·3; N, 8·3. $C_{18}H_{18}O_5N_2$ requires C, 53·2; H, 5·4; N, 8·3%).

γ-L-Glutamylglycine.—Carbobenzyloxy-γ-L-glutamylglycine (0·7 g.) in aqueous methanol was hydrogenated in the normal manner in the presence of palladium black. The filtrate was evaporated under reduced pressure to small volume and excess of ethanol added. After ½ hour, the *γ-L-glutamylglycine* (0·3 g., 74%) was filtered off; after reprecipitation from water with ethanol, it had m. p. 193—194° (Found: C, 41·5; H, 5·9; N, 13·7. $C_7H_{12}O_5N_2$ requires C, 41·2; H, 5·9; N, 13·7%). $[\alpha]_D^{25}$ +11·1° (*c*, 2·52 in water). With ninhydrin at 100° for 15 minutes at pH 2·5, 1·0 mole of carbon dioxide was evolved.

Diethyl Carbobenzyloxy-γ-L-glutamyl-L-glutamate.—Carbobenzyloxy-γ-L-glutamylhydrazide (1 g.) was converted into the azide in chloroform (15 ml.) and added portionwise at 0° to diethyl L-glutamate (from 4 g. of hydrochloride). It was left for some hours at 0° and overnight at room temperature. The solution was washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was dissolved in a little ethyl acetate, and light petroleum added until a little oil separated. The solution was then poured off and excess of light petroleum added to it; the precipitated *diethyl carbobenzyloxy-γ-L-glutamyl-L-glutamate* slowly hardened to a waxy consistency under fresh petroleum. It had m. p. 62—68° (Found: C, 56·1; H, 6·3; N, 6·5. $C_{22}H_{30}O_9N_2$ requires C, 56·6; H, 6·5; N, 6·0%).

γ-L-Glutamyl-L-glutamic Acid.—Diethyl carbobenzyloxy-γ-L-glutamyl-L-glutamate (0·4 g.) was dissolved in N-sodium hydroxide (3 ml.) and left for 2 hours at room temperature. Subsequent treatment in the same manner as in the hydrolysis of carbobenzyloxy-γ-L-glutamylglycine ethyl ester gave carbobenzyloxy-γ-L-glutamyl-L-glutamic acid as an oil which did not crystallise under light petroleum. It was hydrogenated in the usual manner in aqueous methanol, and after evaporation of the filtrate under reduced pressure to 1—2 ml., acetone (10 ml.) was added. *γ-L-Glutamyl-L-glutamic acid* separated as an oil which solidified after some minutes. It was dissolved in water (2 ml.) and acetone (10 ml.) added. After 2 minutes, the supernatant solution was poured off and more acetone (20 ml.) added to it. The acid was filtered off after 1 hour at 0°, and had m. p. 188—191°. Drying at 100°/18 mm. was found necessary to remove water (Found: C, 43·3; H, 6·2; N, 9·8. $C_{10}H_{16}O_7N_2$ requires C, 43·5; H, 5·8; N, 10·1%). $[\alpha]_D^{25}$ <1° (*c*, 1·6 in water), $[\alpha]_D^{25}$ +6° (*c*, 1·1 in water containing 1 mole of hydrochloric acid).

γ-L-Glutamyl-L-aspartic Acid.—The procedure used was as in the preparation of the above dipeptide, but neither diethyl carbobenzyloxy-γ-L-glutamyl-L-aspartate nor carbobenzyloxy-γ-L-glutamyl-L-aspartic acid could be obtained solid. The hydrogenation gave *γ-L-glutamyl-L-aspartic acid* which solidified when kept under acetone. It was dissolved in a little water and fractionally precipitated with acetone. Paper chromatography showed that the first fraction contained a little glutamic acid, but subsequent fractions gave only one spot and had m. p. 177—182°. The product was dried for 2 hours at 100°/18 mm. for analysis, but retained one molecule of water of crystallisation (Found: C, 38·4; H, 5·4; N, 9·5. $C_9H_{14}O_7N_2,H_2O$ requires C, 38·6; H, 5·8; N, 10·0%). $[\alpha]_D^{25}$ +19·5° (*c*, 2·0 in water containing 1 mole of hydrochloric acid).

γ-L-Glutamyl-L-tyrosine.—The procedure used was similar to that for the previous two dipeptides. Carbobenzyloxy-γ-L-glutamyl-L-tyrosine and its ethyl ester were obtained only as shellac-like masses, melting around 70° with loss of gas. *γ-L-Glutamyl-L-tyrosine* crystallised when kept under acetone; after reprecipitation from water with acetone, it had m. p. 219—221°. It was dried at 100°/18 mm. for analysis (Found: C, 53·9; H, 6·0; N, 8·7. $C_{14}H_{18}O_6N_2$ requires C, 54·2; H, 5·8; N, 9·0%). $[\alpha]_D^{25}$ +25·6° (*c*, 2·1 in water).

Carbobenzyloxy-γ-L-glutamylglycylglycine Ethyl Ester.—Carbobenzyloxy-γ-L-glutamylhydrazide (1·2 g.) was converted into the azide in chloroform (20 ml.). This solution was added at 0° to one of glycylglycine ethyl ester (from 4·0 g. of hydrochloride) in chloroform (20 ml.) and left for 2 hours at 0° and overnight at room temperature. The solution was then shaken with dilute hydrochloric acid. *Carbobenzyloxy-γ-L-glutamylglycylglycine ethyl ester* separated slowly from both phases. It was filtered off and recrystallised from hot ethyl acetate, the product (1·3 g., 76%) having m. p. 92—94°. Drying over phosphoric oxide in a vacuum-desiccator gave the *monohydrate* (Found: C, 52·0; H, 6·3; N, 9·3. $C_{19}H_{25}O_8N_3,H_2O$ requires C, 51·7; H, 6·2; N, 9·5%). When dried at 61°/18 mm., the substance liquefied; it solidified again on storage under light petroleum, and was re-dried at 61°/18 mm. (Found: C, 53·4; H, 5·7. $C_{19}H_{25}O_8N_3$ requires C, 53·9; H, 5·9%).

Carbobenzyloxy-γ-L-glutamylglycylglycine.—A solution of carbobenzyloxy-γ-L-glutamylglycylglycine ethyl ester (1·3 g.) in N-sodium hydroxide (7 ml.) was left for 2 hours at room temperature. It was then acidified with 8N-hydrochloric acid and cooled to 0°; after ½ hour *carbobenzyloxy-γ-L-glutamylglycylglycine* (1·0 g., 83%) was filtered off. It had m. p. 100—114°; after recrystallisation from water and washing of the dried product with a little boiling ethyl acetate, the m. p. was 124—127° (Found: N, 10·3. $C_{17}H_{21}O_8N_3$ requires N, 10·6%).

γ-L-Glutamylglycylglycine.—Carbobenzyloxy-γ-L-glutamylglycylglycine (1·0 g.) was hydrogenated in the usual manner in aqueous methanol. After evaporation of the filtrate to small volume under reduced pressure, ethanol was added. After 1 hour at 0°, the *γ-L-glutamylglycylglycine* (0·5 g.) was filtered off. It had m. p. 176—178°, raised by reprecipitation from water by ethanol to 179—180°. It was dried at 100°/18 mm. for analysis (Found: C, 41·3; H, 5·6; N, 15·5. $C_9H_{15}O_6N_3$ requires C, 41·4; H, 6·0; N, 16·1%) and had $[\alpha]_D^{25}$ +9·4° (*c*, 2·75 in water).

Carbobenzyloxy-γ-L-glutamylglycine (Alternative Technique).—Carbobenzyloxy-γ-L-glutamylhydrazide (1·0 g.) was converted into the azide in ethyl acetate (15 ml.) and then added slowly at 0° to a solution of glycine (0·4 g.) and potassium hydrogen carbonate (1·5 g.) in water (10 ml.), stirred mechanically. Stirring was continued for 15 minutes, and the solution left for 2 hours at room temperature. The aqueous layer was acidified and extracted 3 times with an equal volume of ethyl acetate. The combined extracts were washed with a little water, dried (Na_2SO_4), and evaporated under reduced pressure. The remaining carbobenzyloxy-γ-L-glutamylglycine was washed with a little ether and ethyl acetate and collected. Recrystallisation from hot water raised the m. p. from 147—155° to 158—161° (0·45 g., 37%).

R_F *Values of Some γ-L-Glutamyl-peptides.*—Paper partition chromatography, with phenol saturated

with water as the mobile phase in an atmosphere containing ammonia, confirmed the purity of the above γ-glutamyl-peptides and gave the following R_F values: γ-L-glutamyl-glycine 0·20, -L-glutamic acid 0·08, -L-aspartic acid 0·04, -L-tyrosine 0·39, and -glycylglycine 0·24.

Hydrolysis of L-Glutamyl-peptides.—Solutions (*ca.* 1%) of L-glutamyl-peptides were heated in sealed tubes by means of a steam-jacket. Samples were removed at intervals and examined by paper partition chromatography, using phenol saturated with water as the mobile phase in an atmosphere containing ammonia; after being dried, the paper was sprayed with a solution of ninhydrin in moist butanol and the colour developed by heat. With solutions in water and in 0·5*N*-hydrochloric acid, the following results were observed after 24 hours at 100°. The symbols indicate the approximate intensity of the ninhydrin coloration: −, none detected; ±, trace; +, weak; ++, fairly strong; +++, strong; ++++, very strong.

	Aqueous solution.			0·5*N*-Acid solution.		
Dipeptide.	Dipeptide.	Glutamic acid.	Second amino-acid.	Dipeptide.	Glutamic acid.	Second amino-acid.
γ-L-Glutamylglycine	+	−	++++	−	++++	++++
γ-L-Glutamyl-L-tyrosine	+	−	+++	−	++++	+++
γ-L-Glutamyl-L-aspartic acid ...	−	−	++++	−	++++	++++
γ-L-Glutamyl-L-glutamic acid...	+	+++		−	++++	
α-L-Glutamylglycine	+	−	+++	−	+++	++++
α-L-Glutamyl-L-aspartic acid ...	±	−	++++	−	++++	++++
α-L-Glutamyl-L-valine	−	−	−	+	+++	+++
α-L-Glutamyl-L-leucine	±	−	−	+++	+++	+++
α-L-Glutamyl-L-tyrosine	−	−	−	++	+++	+++
α-L-Glutamyl-L-glutamic acid...	−	±		−	++++	

An aqueous solution of glutamic acid, heated for 24 hours at 100°, gave a strong colour in the normal position. Under the same conditions, an aqueous solution of γ-L-glutamylglycylglycine gave: tripeptide, +; glutamic acid, −; glycylglycine, ++; glycine, +. Glycylglycine in 2% acetic acid similarly gave: glycylglycine, ++++; glycine, +.

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THE DYSON PERRINS LABORATORY, OXFORD. [*Received, April* 11*th*, 1950.]

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401. *The Symmetrical Dianthryls. Part IV.*

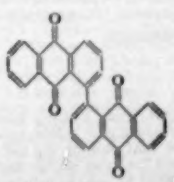
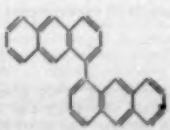
By F. BELL and W. H. D. MORGAN.

1 : 1′-Dianthraquinonyl-4 : 4′-dicarboxylic acid has been resolved into optically active forms. Negative results were obtained on attempting the resolution of naphthidine, 1 : 1′-dinaphthyl-4 : 4′-dicarboxylic acid, and 8 : 8′-diquinolyl.

Some attempts to prepare further compounds exhibiting intramolecular overcrowding are outlined.

STANLEY and ADAMS (*J. Amer. Chem. Soc.*, **1931**, **53**, 2364) attempted the resolution of 1 : 1′-dianthraquinonyl-4 : 4′-dicarboxylic acid. They report that "it was impossible to fractionate the alkaloid salts . . . due to their insolubility," but evidence is given for the uniformity of the quinine salt and also of the dimenthyl ester. The acid was regarded as non-resolvable and a tentative explanation of the result was advanced.

Although the distance between the *meso*-carbon atoms in anthraquinone may be slightly less than that between the *meso*-carbon atoms in anthracene it can scarcely be doubted that the opposition to planarity in 1 : 1′-dianthraquinonyl (I) is considerably greater than in 1 : 1′-dianthryl

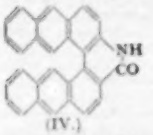
(I.)   (II.)

(II). In Part II (*J.*, **1949**, 1579) it was shown that 1 : 1′-dianthryl exists in enantiomorphous forms of moderate stability. It follows, therefore, that 1 : 1′-dianthraquinonyl and any of its derivatives should exist in enantiomorphous forms, and we were led to repeat the work of Stanley and Adams.

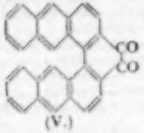
Rather surprisingly the quinidine, morphine, and cocaine salts of 1 : 1′-dianthraquinonyl-4 : 4′-dicarboxylic acid were found to be excessively soluble. The brucine salt could be crystallised from alcohol and slow, but definite, resolution was observed. With cinchonine and cinchonidine, on the other hand, resolution was a facile process and no difficulty was experienced in securing the enantiomorphous forms of the acid with $[\alpha]_D$ +428° and −443°. The optical activity of the acid dissolved in sodium hydroxide was very slowly lost at room temperature, but more rapidly on boiling (complete loss in somewhat over 1 hour's heating). Racemisation was usually made apparent by the sodium salt crystallising from the 1% solution of the acid in 0·1N-sodium hydroxide; the sodium salts of the active forms are much more soluble. The active acids were attacked only slowly by hot thionyl chloride and the resultant chloride was optically inactive. It was, therefore, not possible to prepare the diastereoisomeric menthyl esters.

1 : 1′-Dinaphthyl (III) and 1 : 1′-dianthryl (II) are stereochemically closely related. If normal covalent radii are used the hydrogen atom in position 2 is barely in contact with the

(III.)



(IV.)



(V.)

hydrogen atom in position 8′ (neglecting the van der Waals envelope). Two factors would be likely to render 1 : 1′-dinaphthyl less optically stable than 1 : 1′-dianthryl, *viz.*, the weight factor, for the heavier the moving parts of the molecule the less easy the oscillations about the 1 : 1′-linkage, and, secondly, the buttressing factor, for the presence of the third nucleus must hinder the outward movement of the 9 : 9′-hydrogen atoms in a dianthryl. Nevertheless it appears possible that 1 : 1′-dinaphthyl might be obtained in enantiomorphous forms. The most direct route to such optically active dinaphthyls appeared to be the elimination of the amino-groups from the optically active 2 : 2′-diamino-1 : 1′-dinaphthyls already described (Kuhn and Goldfinger, *Annalen*, 1929, **470**, 183). This, however, did not prove to be the case as conditions could not be found for smooth elimination. Next, resolution of 4 : 4′-diamino-1 : 1′-dinaphthyl by (+)-camphorsulphonic acid and of 1 : 1′-dinaphthyl-4 : 4′-dicarboxylic acid by brucine was attempted. The results were completely negative and, therefore, the resolvability of 1 : 1′-dinaphthyl must remain an open question.

Kuhn and Albrecht (*ibid.*, 1928, **464**, 91) resolved 1 : 1′-dianthraquinonyl-2 : 2′-dicarboxylic acid by means of quinine. It is now found that this resolution is more easily accomplished by use of quinidine. The exceptionally high optical stability of the enantiomorphous forms is confirmed. In this compound the carboxyl groups must form almost insuperable obstacles to the opposed carbonyl groups. This opposition is of course lacking in the isomeric 1 : 1′-dianthraquinonyl-4 : 4′-dicarboxylic acid.

The optical stability and high rotatory power of these compounds renders them promising starting materials for the preparation of systems such as (IV) and (V) which might be expected to be non-planar owing to intramolecular overcrowding. Compound (IV) might arise from a Hofmann reaction on the amide derived from the anhydride of 1 : 1′-dianthryl-2 : 2′-dicarboxylic acid. We failed to prepare the requisite anhydride. A compound of type (V) might be formed by the interaction of the chloride of 1 : 1′-dianthryl-2 : 2′-dicarboxylic acid with metals, or of the ester with sodium (acyloin condensation) or 2 : 2′-diformyl-1 : 1′-dianthryl with potassium cyanide. The results of experiments along these lines were negative.

Experimental.

(M. p.s are uncorrected.)

1 : 1′-Dianthraquinonyl-4 : 4′-dicarboxylic acid was prepared from 1-chloro-4-benzamidoanthraquinone by the method of Stanley and Adams (*loc. cit.*), and formed a pale yellow powder, m. p. 418°. The resolution with brucine was unsatisfactory but, nevertheless, that part of the salt which was least soluble in absolute alcohol gave an acid of small lævorotation, and the more soluble salt gave an acid of small dextrorotation. Resolution was however readily accomplished by use of cinchonine, which gave a less soluble salt of the (−)-acid, or cinchonidine, which gave a less soluble salt of the (+)-acid. The following is a typical experiment. Cinchonine (6 g., 2 mols.) was added to a suspension of the acid (5 g., 1 mol.) in boiling absolute alcohol (500 c.c.). About half of the acid rapidly dissolved but to get the remainder into solution required the addition of a further 3 g. of cinchonine. No crystallisation occurred on cooling of the solution and for this it was necessary to reduce the volume to about 100 c.c.

The first crop consisted of almost pure cinchonine (3 g.), the second crop of bright yellow crystals (6 g.), and the filtrate from this was decomposed by pouring it into boiling dilute hydrochloric acid. The recovered acid ([α]$_D$ about +350° in 0·1N-sodium hydroxide) was purified by combination with cinchonidine (below).

The crop of cinchonine salt was recrystallised from alcohol until of constant rotatory power, [α]$_D^{25}$ +20° (*c*, 1·01 in chloroform), and then had m. p. 207° (decomp.). Decomposition gave (−)-**1** : 1′-dianthraquinonyl-**4** : 4′-dicarboxylic acid, m. p. 395°, [α]$_D$ −443° (*c*, 1·02 in 0·1N-sodium hydroxide).

The (+)-acid (3·15 g., 1 mol.; see above) was added to a boiling solution of cinchonidine (5·7 g., 3 mols.) in absolute alcohol (250 c.c.). The liquid immediately filled with a heavy crystalline deposit of the cinchonidine salt. This was purified by repeated extraction with hot alcohol. The purified salt, m. p. 234° (decomp.), furnished (+)-**1** : 1′-dianthraquinonyl-**4** : 4′-dicarboxylic acid, m. p. 390°, [α]$_D$ +428° (*c*, 1·04 in 0·1N-sodium hydroxide).

The sodium salts of the active acids were very much more soluble than was the sodium salt of the inactive acid, a 1% solution of which tended to crystallise in the polarimeter tube. At room temperature the solutions of the sodium salts slowly lost activity (the observed rotation had fallen to about one-third after 70 hours); at the b. p. the same loss was attained in somewhat under 1 hour. The active acid required some 6 hours' heating with thionyl chloride for complete dissolution. The chloride left after removal of the excess of thionyl chloride was insoluble in benzene, chloroform, carbon tetrachloride, acetone, *o*-dichlorobenzene, or methyl ethyl ketone, and was inactive in pyridine (*c*, 0·99).

Resolution of **1** : 1′-*Dianthraquinonyl*-**2** : 2′-*dicarboxylic Acid*.—Quinidine (36·5 g.) was added to the acid (24·5 g.) in boiling alcohol (1600 c.c.). The mixture, after boiling for 1 hour, was allowed to cool overnight and the crystalline crop filtered off and well washed with alcohol. The residue (23·7 g.) was repeatedly extracted with hot alcohol to remove more soluble materials, and the final residue (21·2 g.) decomposed by trituration with dilute hydrochloric acid. The material so obtained crystallised from acetic acid in compact orange-red prisms, [α]$_{5791}$ −318° (*c*, 2·6 in 0·1N-sodium hydroxide). The alcoholic filtrate from this salt was evaporated to about one-eighth bulk and the crop (4·8 g.) obtained on cooling filtered off. The alcoholic filtrate was poured slowly into boiling dilute hydrochloric acid whereupon there was obtained the (+)-acid, [α]$_{5791}$ +304° (*c*, 2·5 in 0·1N-sodium hydroxide).

The acid was not decarboxylated when it was boiled with quinoline for 4 hours.

The acid was converted by thionyl chloride into the chloride which was used in the following experiments.

(i) The chloride [from 2 g. of (−)-acid], benzene (40 c.c.), and sodium azide (3 g.) were heated under reflux for 6 hours. Sodium hydroxide (3 g. in 25 c.c. of water) was then added and the heating continued for 2 hours. The benzene was removed in steam, and the residual solution filtered from a black highly insoluble material. The filtrate on acidification gave 1·7 g. of acid, [α]$_{5791}$ −310° (*c*, 2·6 in 0·1N-sodium hydroxide).

(ii) Sodium (0·8 g.) was added to the chloride (from 3·4 g. of acid) in boiling xylene. The sodium became covered by a black layer and little action appeared to take place. The majority of the acid was recovered unchanged after alkaline decomposition.

(iii) A similar experiment with zinc gave equally negative results.

1 : 1′-*Dianthryl*-**2** : 2′- *dicarboxylic Acid*.—This was not decarboxylated by boiling it with quinoline for 4 hours. The acid chloride in boiling xylene with copper powder or finely divided silver gave *amphi-iso*pyranthrone as the only product of change.

The (−)-acid (1 g.) in acetic anhydride was boiled for 1 hour. The solution did not crystallise on cooling, so all the acetic anhydride was removed under reduced pressure. The residual bright yellow scales, darkening at 230° and almost black at 250°, could not be purified by crystallisation. Only the original acid was recovered by treatment with aqueous ammonia (*d* 0·880); the acid had undergone considerable racemisation. The (−)-acid was converted through the chloride into the ethyl ester, which crystallised from ethanol in yellow flocks, m. p. 177—180°, [α]$_D$ −373° (*c*, 1 in chloroform). The ester (3·5 g.) was added to powdered sodium (1 g.) in xylene, and the mixture boiled for 1 hour. The sodium almost immediately became black but otherwise little reaction occurred. After decomposition the majority of the ester was recovered as the fully active (−)-acid, whilst the blue-black residue had the appearance of *amphi-iso*pyranthrone.

8 : 8′-*Diquinolyl*.—This was prepared by the method of Niementowski and Seifert (*Ber.*, 1905, **38**, 762). The base (1 mol.) did not dissolve in tartaric acid (1 mol.) in ethanol. With tartaric acid (2 mols.) a non-crystallising solution was obtained.

With (+)-camphorsulphonic acid a highly crystalline salt was obtained. This could be recrystallised from alcohol without change of m. p. (250°) or rotatory power {[α]$_{5461}$ +19·7° (*c*, 1·22 in chloroform)}. The **8** : 8′-diquinolyl recovered from all crops was completely inactive.

4 : 4′-*Diamino*-**1** : 1′-*dinaphthyl* (*Naphthidine*).—This amine was prepared from **1** : 1′-azonaphthalene by reduction with stannous chloride and treatment of the product with concentrated hydrochloric acid (Cohen and Oesper, *Ind. Eng. Chem., Anal.*, 1936, **8**, 306). Several attempts to prepare the compound from α-naphthylamine (Sah and Yuin, *Rec. Trav. chim.*, 1939, **58**, 751) gave very unsatisfactory yields.

Naphthidine has been described as "a compound fairly soluble in organic solvents." This statement is rather misleading as the solubility is about 1% in either boiling absolute alcohol or boiling benzene, and the compound separates again on cooling. For the following experiments the naphthidine was recrystallised from absolute alcohol (1 l. for 8 g.) (charcoal).

Naphthidine did not yield a salt with tartaric acid. When (+)-camphorsulphonic acid (0·9 g., 2 mols.), dissolved in alcohol, was added to naphthidine (0·56 g., 1 mol.) dissolved in absolute alcohol (70 c.c.) an immediate pink coloured precipitate formed which was insoluble in the common solvents. This salt was repeatedly extracted with alcohol, and the residue (m. p. 263° (decomp.), [α]$_D$ +31·5° (*c*, 2·03 in pyridine)) decomposed by trituration with dilute aqueous ammonia. The liberated base was optically inactive.

1 : 1′-*Dinaphthyl*-**4** : 4′-*dicarboxylic Acid*.—This acid, m. p. 348°, was prepared from naphthidine by the method of Seer and Scholl (*Annalen*, 1913, **398**, 83), the only modification being that the **4** : 4′-di-

cyano-1 : 1'-dinaphthyl was separated from the inorganic material by extraction with chloroform and hydrolysed with ethylene glycol–potassium hydroxide (10 c.c. of 10% solution per g.) for 15 hours.

Attempts to resolve the acid using quinidine, morphine, cinchonine, and cinchonidine failed owing to the high solubilities of the salts. Brucine gave a crystalline salt which after recrystallisation from alcohol had m. p. 215°, $[\alpha]_D$ −17·9° (*c*, 2·35 in chloroform). The brucine salt did not exhibit mutarotation; the recovered acid was completely inactive.

2 : 2'-*Diamino*-1 : 1'-*dinaphthyl*.—Deamination of the racemic compound, prepared by the method of Kuhn and Goldfinger (*loc. cit.*), was unsuccessful, using (*a*) the procedure applied to 2 : 2'-diamino-1 : 1'-dianthryl (*J.*, 1949, 1582), (*b*) alcohol, (*c*) sodium stannite, or (*d*) cuprous oxide–alcohol (Hodgson and Turner, *J.*, 1942, 748). No definite compounds were isolated (cf. previous work by Corbellini, *Atti R. Accad. Lincei*, 1931, **14**, 341).

2 : 2'-*Diformyl*-1 : 1-*dianthraquinonyl*.—Crude 2 : 2'-bisdibromomethyl-1 : 1'-dianthraquinonyl (rosettes, m. p. 336°, from o-dichlorobenzene) was converted as previously described (*J.*, 1949, 1580) into crude 2 : 2'-diformyl-1 : 1'-dianthraquinonyl. The reddish amorphous material (30 g.) was extracted with aqueous sodium carbonate solution (2 l. of 5%), and the residue dried (35 g.). This was dissolved in chloroform and the filtered solution evaporated to 50 c.c. The fawn-coloured dialdehyde which separated had m. p. 313°. Owing to its insolubility it was not possible to submit it to the action of potassium cyanide under favourable conditions: only tarry products were obtained.

The authors are indebted to Mr. W. Smith, F.R.I.C., and Imperial Chemical Industries Limited (Dyestuffs Division), for a gift of 1-chloro-4-benzamidoanthraquinone and to the Department of Scientific Industrial Research for a grant to one of them (W. H. D. M.).

College of Technology, Belfast. [*Received, April 6th*, 1950.]

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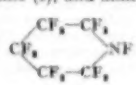
402. *The Fluorination of Organic Compounds Containing Nitrogen.*

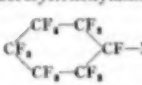
By R. N. Haszeldine.

The fluorination of pyridine and aniline by the cobalt fluoride and catalytic methods yields the non-basic perfluoropiperidine and perfluoro*cyclo*hexylamine, respectively. The fluorination of dimethylaniline gives perfluoro*cyclo*hexane, perfluorodimethylamine, and possibly perfluorodimethyl*cyclo*hexylamine. Methylaniline similarly yields perfluoro*cyclo*hexane and perfluoromethylamine; the latter compound, which is non-basic, is also obtained by the passage of methylamine over cobalt trifluoride.

The fluorination of hydrocarbons has been achieved by several methods, notably those involving fluorine itself in the presence of a "catalyst" (Bigelow, *Chem. Reviews*, 1947, **40**, 51; Haszeldine and Smith, *J.*, in press; Grosse and Cady, *Ind. Eng. Chem.*, 1947, **39**, 290), the use of cobalt trifluoride (Fowler *et al.*, *Ind. Eng. Chem.*, 1947, **39**, 292; Haszeldine and Smith, forthcoming communication), and more recently the electrolysis of compounds dissolved in anhydrous hydrogen fluoride (Simons, *J. Electrochem. Soc.*, 1949, **95**, 47; and Abstracts, 116th Meeting, American Chemical Society, Sept. 1949). The unusual properties associated with the products are well-established (Smith, *Ann. Reports*, 1947, **44**, 86). Apart from a recent note (Haszeldine, *J.*, 1950, 1638), the successful direct fluorination of heterocyclic nitrogen compounds or of aromatic amines has not been described. Simons (*loc. cit.*), for example, has reported that the electrolysis of pyridine in anhydrous hydrogen fluoride yields perfluoropentane and nitrogen trifluoride.

The fluorination of pyridine, aniline, and dimethylaniline, and preliminary results with methylaniline and methylamine, are described in the present communication. Both the cobalt fluoride and the catalytic methods of fluorination were used successfully, although the yields of the corresponding perfluoro-compounds were extremely low. Pyridine was converted into perfluoropiperidine (I), and aniline yielded perfluoro*cyclo*hexylamine (II).

(I.) 

 (II.)

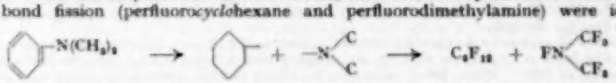
The vapour-phase fluorination of basic compounds is difficult, probably because of the formation of a non-volatile hydrofluoride when the entering gas stream encounters hydrogen fluoride produced during the fluorination. This can be overcome to some extent by carrying the organic compound to be fluorinated in a stream of nitrogen, which also sweeps out the hydrogen fluoride formed. The basicity and tendency for hydrofluoride formation to occur is steadily reduced, whilst the volatility is increased as fluorine is introduced into the molecule,

and it is the initial reaction which is important in determining the yield. The fluorination of heterocyclic compounds or of aromatic amines which already contain fluorine should give yields much superior to those recorded here. The bisfluoromethylpyridines (McBee, Hass, and Hodnett, *Ind. Eng. Chem.*, 1947, **39**, 389), tristrifluoromethyltriazine (McBee, Pierce, and Bolt, *Ind. Eng. Chem.*, 1947, **39**, 391) and 2-fluoropyridine (Hawkins and Roe, *J. Org. Chem.*, 1949, **14**, 328) are examples of such non-basic compounds.

The elimination of the nitrogen atom in pyridine during fluorination was shown by the isolation of the straight-chain fluorocarbon, C_5F_{12}. Other compounds, in which carbon–carbon bond fission instead of carbon–nitrogen bond fission had occurred, were also present in the reaction products but were not separated. Perfluoropiperidine is non-basic, and preliminary examination suggests that it has a stability similar to that of the fluorocarbons. Whether there is any specific reactivity associated with the N–F bond has yet to be determined; Ruff and Giese (*Ber.*, 1936, *B*, **69**, 598), for example, postulated that mercury attacks the N–F link in compounds such as $CF_2{\cdot}NF{\cdot}NF{\cdot}CF_2$. Relative to pyridine or piperidine, perfluoropiperidine has a low boiling point and refractive index, and a high density. These values—b. p. 49—50°, n_D^{20} 1·279, d_4^{20} 1·738—are similar to those of comparable fluorocarbons (C_6F_{12}, a solid, sublimes at 52°; C_7F_{14}, b. p. 76·2°, n_D^{22} 1·276, d_4^{22} 1·784).

The fluorination of aniline yielded perfluoro*cyclo*hexane as well as the non-basic perfluoro*cyclo*hexylamine, and showed that appreciable carbon–nitrogen bond fission with subsequent complete fluorination of the ring had occurred. Perfluoro*cyclo*hexylamine has a boiling point close to that of perfluoromethyl*cyclo*hexane, and the density and refractive index are only slightly higher. Thus, the replacement of carbon by nitrogen to produce a compound with one less fluorine atom scarcely alters these physical properties.

The fission of the carbon–nitrogen bond during the fluorination of aniline produced perfluoro*cyclo*hexane and presumably nitrogen trifluoride, although the latter compound was not identified. When dimethylaniline was fluorinated, however, both products from the carbon–nitrogen bond fission (perfluoro*cyclo*hexane and perfluorodimethylamine) were identified:



Perfluorodimethylamine has been prepared recently in these laboratories (Emeléus and Thompson, *J.*, 1949, 3080) by the fluorination of trimethylamine. Perfluorodimethyl*cyclo*hexylamine was not definitely identified. The fluorination of methylaniline followed a similar course, and perfluoro*cyclo*hexane and perfluoromethylamine were isolated. The latter compound, which is also obtained by the direct fluorination of methylamine, was claimed by Ruff and Giese (*loc. cit.*) as one of the products from the fluorination of silver cyanide, but these authors were unable to effect its separation from hexafluoroethane. Perfluoromethylamine and perfluorodimethylamine are both non-basic compounds which are stable to dilute aqueous alkali. These and the compounds described earlier contain electronegative fluorine atoms and trifluoromethyl groups attached to a nitrogen atom, and should not strictly be termed amines; they are more related to the inert nitrogen trifluoride. It should eventually be possible to synthesise complete series of compounds [*e.g.*, $NH(CH_3)_2$, $NH(CF_3)(CH_3)$, $NH(CF_3)_2$, $NF(CF_3)_2$] of steadily decreasing basicity and reactivity.

Experimental.

The Cobalt Fluoride Apparatus.—The compound to be fluorinated was added as a liquid or passed as a gas into a steel preheater, 12″ long and of 2″ internal diameter, heated electrically to 200° or 250° depending upon the boiling point of the compound. A stream of dry nitrogen was admitted through a second inlet tube, and the organic vapour was thereby carried into a second furnace, 48″ long and of 2″ internal diameter, containing cobalt trifluoride. The cobalt trifluoride was prepared *in situ* by the passage of fluorine over trays of cobalt difluoride (2500 g.) heated to 350° until a strong positive test for fluorine was obtained at the exit. At the end of an experiment, the cobalt trifluoride was regenerated. Since profound decomposition occurred during most of the experiments described here, and since complete fluorination was desired, considerably less of the organic compound was added than that which could theoretically be caused to react with the available fluorine (500 g.). At the end of the experiment, and half way through those experiments in which comparatively large amounts of material were fluorinated, addition of the organic compound was stopped, the temperature of the vessel was raised to 450°, and the apparatus was shaken vigorously by two vibro-shakers whilst nitrogen was swept through the apparatus for two hours to remove and fluorinate any hydrofluorides formed during the reaction. Appreciable quantities of product were thereby obtained. The temperature was then re-adjusted, and the experiment continued. The reaction temperatures and conditions quoted below are not necessarily the best, and variation in the conditions would probably lead to improved yields.

The Catalytic Fluorination Apparatus.—A vertical steel tube, 24" long and of 2" internal diameter, was filled with gold-plated copper turnings, and heated electrically. The vapour of the organic compound, diluted by nitrogen, and fluorine, also diluted by nitrogen, were passed into the vessel through diametrically-opposed tubes situated 2" from its top. The exit gases from the reactor base were collected in a series of cooled traps. The apparatus was similar in design to that described by Hasszeldine and Smith (*loc. cit.*); see also Cady and Grosse (*loc. cit.*).

Fluorination of Pyridine by Means of Cobalt Trifluoride.—Pyridine (50 g.) was passed at a rate of 10 ml./hour over cobalt trifluoride heated to 350°; the nitrogen dilution was 10 l./hour. The product collected in the traps was allowed to warm slowly to room temperature and, by being heated on a boiling-water bath in a stream of nitrogen, the material of b. p. <100° was passed through a copper tube, 24" long, packed with sodium fluoride pellets and heated electrically at 100°. The products from six such experiments (47·3 g.), now free from hydrogen fluoride, were distilled from sodium fluoride and phosphoric oxide through an efficient fractionating column. Apart from an unidentified, nitrogen-containing fraction, b. p. 75—77° (0·8 g.), the only plateau on the distillation curve of the material boiling below 100° was that due to *perfluoropiperidine* (2·1 g., 0·2%) (Found: C, 20·6; N, 4·1; F, 73·2%; *M*, 283. C_5NF_{11} requires C, 21·2; N, 5·0; F, 73·8%; *M*, 283). Perfluoropiperidine, b. p. 49—50°, n_D^{25} 1·279, d_4^{25} 1·738, has a characteristic musty smell.

Fluorination of Pyridine by the Catalytic Method.—Pyridine (4 g./hour), diluted with nitrogen (8 l./hour), was passed into the reaction vessel, heated to 280°. Fluorine (10 g./hour), diluted with nitrogen (8 l./hour), was admitted simultaneously. After a total operating time of 24 hours, 101 g. of pyridine had been added. The product boiling below 100° was passed over sodium fluoride as described above, and taken into a vacuum system for examination. Repeated fractionation afforded perfluoropiperidine (0·9 g., 0·3%), n_D^{25} 1·278 (Found: *M*, 282), and a fraction (1·3 g.) corresponding to perfluoropentane, b. p. 29° (Found: *M*, 290. Calc. for C_5F_{12}: *M*, 288). Simons (*loc. cit.*) reports b. p. 27—28°.

Fluorination of Aniline by Means of Cobalt Trifluoride.—Aniline (40 g.) was added to the reaction vessel, heated to 300°, at a rate of 6 ml./hour and nitrogen (10 l./hour) was passed in simultaneously. The products (53·4 g.) from five such experiments were combined and passed, in a slow stream of nitrogen, through a tube of sodium fluoride pellets heated to 120°. The condensed liquid was distilled through an efficient column, and two fractions were identified. (*a*) A compound solidified in the condenser (thermometer temperature 50—52°). It was taken into the vacuum system, fractionated further, and found to be perfluoro*cyclo*hexane (2·2 g., 0·3%), subliming at 50—52° (Found: *M*, 298. Calc. for C_6F_{12}: *M*, 300). In view of the well-known difficulty of purifying this compound the yield was undoubtedly much higher than indicated here. (*b*) *Perfluorocyclohexylamine* (1·7 g., 0·2%), b. p. 75—76°, n_D^{25} 1·286, d_4^{25} 1·787 (Found: C, 21·7; N, 3·9; F, 73·5%; *M*, 332. C_6NF_{13} requires C, 21·6; N, 4·2; F, 74·2%; *M*, 333).

Fluorination of Aniline by the Catalytic Method.—Aniline (2 g./hour), diluted with nitrogen (6 l./hour), was allowed to react with fluorine (10 g./hour), diluted with nitrogen (6 l./hour), on the surface of the catalyst heated to 290°. When 100 g. of aniline had been passed, the total product was treated with sodium fluoride, as described earlier, and distilled. Perfluoro*cyclo*hexane (1·7 g.; *M*, 297) and perfluoro*cyclo*hexylamine (0·7 g.; *M*, 330) were again isolated. No attempt was made to investigate the material which boiled below room temperature.

Fluorination of Dimethylaniline by Means of Cobalt Trifluoride.—Dimethylaniline (50 g.) was added to the reaction vessel heated to 300° over a period of 12 hours. A nitrogen flow of 10 l./hour was used. The products from two such experiments, freed from hydrogen fluoride as described above, were separated into two portions: (*a*) The material boiling below 80°, which constituted the bulk of the product, and was taken into the vacuum system for examination. Exhaustive fractionation yielded perfluoro*cyclo*hexane (1·1 g.), identified as described earlier, and perfluorodimethylamine, b. p. −38° (Found: F, 77·0%; *M*, 170. Calc. for C_2NF_7: F, 77·8%; *M*, 171). Emeléus and Thompson (*loc. cit.*) report b. p. −37·0°. The yield of pure compound was 1·3 g., but an appreciable quantity was lost by the fractionation procedure. Perfluorodimethylamine, which has a musty odour, was not absorbed by 5*N*-hydrochloric acid or hydrolysed by 5*N*-alkali at room temperature. (*b*) The material, b. p. >80°, was distilled. A fraction (1·05 g.), b. p. 116—120°, n_D^{25} 1·305, was possibly perfluorodimethyl*cyclo*hexylamine (Found: N, 3·0%; *M*, 428. C_9NF_{17} requires N, 3·2%; *M*, 433). Insufficient material was available for full identification.

Fluorination of Methylaniline.—The fluorination of methylaniline (50 g.), as described for dimethylaniline, gave *perfluoromethylamine*, b. p. −75°, amongst the volatile products (Found: N, 11·4; F, 77·6%; *M*, 120. CNF_5 requires N, 11·6; F, 78·4%; *M*, 121). Ruff and Giese (*loc. cit.*) report b. p. −80° for a fraction believed to contain CF_3NF_2 and C_2F_6. A fraction which might correspond to perfluoromethyl*cyclo*hexylamine could not be isolated from the small amount of material, b. p. >80°, available for examination. Perfluoro*cyclo*hexane was again detected.

The Fluorination of Methylamine.—Methylamine (20 g.) passed over cobalt trifluoride at 190° gave a product which contained perfluoromethylamine, b. p. −75°; *M*, 120. This compound is not decomposed by 5% sodium hydroxide or absorbed by 5*N*-hydrochloric acid; it has a characteristic musty odour.

The author is indebted to Professor M. Stacey and Dr. F. Smith in whose laboratory he first attempted the fluorination of pyridine.

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NOTES.

Miscellaneous Sulphones. By K. Bowden and C. H. Reece.

During recent investigations certain sulphones were required as intermediates. As three of these were new, and the known compounds were prepared by improved methods, it seems desirable to record the following data.

4-Nitro-4′-acetamidodiphenyl Sulphone.—4-Nitro-4′-acetamidodiphenyl sulphide (63 g.) was dissolved in glacial acetic acid (250 c.c.) and cooled to 90°. Hydrogen peroxide (95 c.c. of "100-vol.") was added during 45 minutes with stirring under reflux and the mixture then boiled for a further 30 minutes. On cooling, the sulphone (70 g., 100%), m. p. 224°, crystallised. Raizins *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 2763) obtained the sulphone in 81% yield by a rather cumbersome method using potassium dichromate and sulphuric acid.

4 : 4′-Diacetamidodiphenyl Sulphone.—This was similarly prepared (yield, 73%) from 4 : 4′-diacetamidodiphenyl sulphide and had m. p. 282°. Raizins *et al.* (*loc. cit.*) record a 63% yield.

4-Acetamido-4′-hydrazinodiphenyl Sulphone.—To concentrated sulphuric acid (200 c.c.) at 0° was slowly added sodium nitrite (16 g.) with stirring. The mixture was then carefully warmed to 50°, held at this temperature until all the sodium nitrite had dissolved, and again cooled to 0°. 4-Amino-4′-acetamidodiphenyl sulphone (38 g.) was then added during 45 minutes and stirring continued for a further 15 minutes, after which acetic acid (50 c.c.) was added dropwise at < 10° and the mixture stirred for 2 hours at this temperature. The solution was poured on ice (500 g.), and excess nitrous acid destroyed with urea. The diazonium solution so obtained was reduced by adding it to a solution of stannous chloride (150 g.) in concentrated hydrochloric acid (300 c.c.) cooled to 5°. The resultant precipitate, after being crystallised from hot water (300 c.c.), was dissolved in water (500 c.c.) and converted into the free *hydrazine* with aqueous ammonia. The compound crystallised from alcohol as yellow needles, m. p. 210° (4 g., 10%) (Found : C, 55·2; H, 5·0; N, 13·0. $C_{14}H_{15}O_3N_3S$ requires C, 55·1; H, 5·0; N, 13·7%).

4 : 4′-Dihydrazinodiphenyl Sulphone.—4 : 4′-Diaminodiphenyl sulphone (20 g.) was dissolved in concentrated hydrochloric acid (40 c.c.) and water (60 c.c.) and the hot solution poured on ice (100 g.) to precipitate the hydrochloride. This mixture was cooled to 0° and sodium nitrite (15 g.) in water (50 c.c.) added dropwise with stirring during 30 minutes, the temperature being kept below 10°. The solution was then stirred below 10° for 1 hour and excess of nitrous acid destroyed with urea. Reduction was effected by slowly adding the solution to stannous chloride (85 g.) in concentrated hydrochloric acid (170 c.c.) at 5°. The resulting precipitate was crystallised from dilute hydrochloric acid and converted into the free *hydrazine* with aqueous ammonia. The compound crystallised from water as colourless needles, m. p. 190° (slight decomp.) (8 g., 36%) (Found : C, 52·1; H, 5·1; N, 19·3. $C_{12}H_{14}O_2N_4S$ requires C, 51·8; H, 5·1; N, 20·1%).

The dihydrazine (5 g.) in glacial acetic acid (15 c.c.) and water (15 c.c.) was cooled to 10° and a solution of acetone (4 c.c.) in water (6 c.c.) added with stirring. After a further 30 minutes' stirring the precipitated *diisopropylidene* derivative was filtered off, and crystallised from alcohol as bright yellow needles, m. p. 232° (decomp.) (Found : C, 59·6; H, 6·2; N, 14·8. $C_{18}H_{22}O_2N_4S$ requires C, 60·3; H, 6·2; N, 15·6%).—The University, Leeds, 2. [*Received, May 5th*, 1950.]

The Determination of Fluorine in Organic Compounds. By J. F. Ellis and W. K. R. Musgrave.

In adapting Willard and Winter's titration of fluoride by thorium nitrate (*Ind. Eng. Chem. Anal.*, 1933, **5**, 7) to the determination of fluorine in organic compounds, Musgrave and Smith (with Tatlow, *J.*, 1949, 3026) achieved a reproducible end point by filtering off the bulk of the thorium fluoride before completing the titration. In addition, the observation by Stross (*Metallurgia*, 1947, **36**, 346) and Milton *et al.* (*Analyst*, 1947, **72**, 43) that the introduction of starch prevents the precipitation of thorium fluoride and so eliminates the necessity for the filtration, was confirmed by one of us (W. K. R. M.). Neither Stross nor Milton *et al.* gave details, and it has been found that in the presence of the products of fusion of an organic compound certain precautions have to be taken. The following method has now been found satisfactory.

To an aliquot containing not more than 10 mg. of fluoride ion, add 1 ml. of 0·05% aqueous sodium alizarinsulphonate and discharge any purple colour by dropwise addition of 2*N*-nitric acid. Add 5 ml. of half-neutralised chloroacetic acid as buffer and 5 ml. of 5% starch solution (previously filtered through Whatman No. 3 paper). Dilute the solution to 100 ml. and titrate it with 0·05*N*-thorium nitrate solution. At the end-point the colour in the solution changes from pale yellow to pink.

It is essential to use freshly prepared starch solution for its efficacy is lost after about 12 hours. Further, its action as a protective colloid for thorium fluoride is not indefinite in duration and this is precipitated if the titration is not completed quickly, preferably within one minute.

In applying this method to solutions containing alcohol and sodium cyanide, hydroxide, chloride, and sulphide, it was found that the first two have to be removed (see Table I). The alcohol, which causes premature precipitation of thorium fluoride, is eliminated by evaporating the solution to one-tenth of its volume, adding water, and repeating the evaporation. The cyanide ion, which depresses the end-point slightly, is removed by precipitation from the slightly acid (HNO_3) solution by adding a slight excess of *N*-silver nitrate. The excess of silver ion is removed by adding a little *N*-sodium chloride so as to prevent reaction with the buffer, and the precipitates are filtered off on a No. 40 paper after coagulation at 70°. Sulphide ion, if present, is precipitated with the silver cyanide and chloride in a very fine state which passes through the filter, and the precipitate, in this case, must be removed by centrifuging and decantation through a No. 40 filter.

TABLE I.

(All solutions contained 25 ml. of 0·1035N-NaF in 500 ml.; 50-ml. aliquots were taken.)

Additional : ml. of N-soln.	$Th(NO_3)_4$, N.	Vol. of $Th(NO_3)_4$: found.	calc.
NaOH, 60	0·0474	5·46, 5·46 •	5·46
,, 60; NaCN, 10	0·0474	5·43, 5·43	5·46
,, 50; ,, 5	0·0419	6·15, 6·15	6·18
,, 50; ,, 2	0·0419	6·16, 6·16	6·18
,, 50; NaCl, 2	0·0419	6·18, 6·18	6·18
,, 50; ,, 10	0·0419	6·18, 6·18	6·18
,, 50; ,, 20	0·0419	6·18, 6·18	6·18
,, 60; Na_2S, 10	0·0474	5·46, 5·46	5·46

• When the solution used in this titration contained 50% of alcohol, 5·25 ml. of 0·0474N-$Th(NO_3)_4$ were required (calc.: 5·46 ml.) and the end-point was obscure.

After removal of the interfering ions the buffer and starch solutions are added (the indicator and nitric acid having been added previously), and the solutions made up to 100 ml. and titrated with thorium nitrate. As a result the titration figures are restored to the correct values.

Application of the method to organic compounds gave the results shown in Table II. The fusions were carried out upon 50—100 mg. of the compound in a nickel bomb. The fusion solution was made up to 100 ml. after removal of the alcohol, and an aliquot containing about 5 mg. of fluoride ion was taken. If only a small quantity of the compound was available, 15—20 mg. were used and the whole of the fusion solution was used in one titration.

TABLE II.

[0·0419N-$Th(NO_3)_4$ was used except for the determination denoted by an asterisk, for which 0·0474N-$Th(NO_3)_4$ was used.]

Compound.	Wt. of sample (g.).	Vol. of $Th(NO_3)_4$ (ml.).	F, % : found.	calc.
C_7F_{14}	0·01562	2·98, 2·99	75·8	76·0
$C_2F_3Cl_3$	0·05082	2·38, 2·38	18·6	18·62
$C_2F_3Cl_3$	0·01847	1·40, 1·40	30·2	30·4
	0·05303	4·07, 4·06	30·3	30·4
$C_7H_2O_2N_3F_3$	0·10030 •	6·14, 6·14	27·5	27·65
	0·06995	4·84, 4·83	27·55	27·65
	0·09674	6·68, 6·70	27·5	27·65
$C_{11}H_5O_3NClF_3$	0·07792	3·98, 4·00	20·40	20·40
	0·07576	3·85, 3·84	20·25	20·40
	0·02158	5·47	20·25	20·40
$C_9H_4O_4NSF_3$	0·08454	4·26, 4·26	20·0	20·10
	0·08918	4·48, 4·48	19·95	20·10
	0·08078	4·06, 4·07	20·0	20·10

The authors thank Imperial Chemical Industries Limited for supplying materials.—THE UNIVERSITY, SOUTH ROAD, DURHAM. [*Received, March 20th*, 1950.]

The Double Salts, Sodium Cobalt Sulphate and Sodium Magnesium Sulphate. By HENRY BASSETT and (the late) JOSEPH H. HENSHALL.

THE following experiments were carried out some years ago in an endeavour to throw further light on the conditions under which replacement of $M''(H_2O)_4$ by $Na_2(H_2O)_2$ in hydrated salts appears to be possible. The most striking instances of this type of replacement had been found in the systems $NaCl$-$NiCl_2$-$CdCl_2$-H_2O and $NaCl$-$CoCl_2$-$CdCl_2$-H_2O (Bassett, Henshall, Sergeant, and Shipley, *J.*, 1933, 646).

A complete explanation of the phenomena can only be expected from an *X*-ray study of the double salts concerned, but this is not available and offers difficulties. Isomorphous replacement by cations of different valency associated with compensatory changes in hydration has been established in certain cases, notably for the alunites and jarosites (Hendricks, *Amer. Min.*, 1937, **22**, 772; Bassett and Goodwin, *J.*, 1949, 2253).

Since the well-known double sulphates $Na_2SO_4.M''SO_4.4H_2O$ may contain an ion $[M''(H_2O)_4]''$ it seemed possible that careful examination of such compounds might show that their composition was somewhat variable owing to some replacement of the type mentioned above. Much phase-rule work has been carried out on the compounds of this group but the information available in the literature on the point under discussion is scanty and somewhat contradictory. In many cases the double salts have only been analysed after crystallisation from solutions containing the constituents in equimolecular proportions, while in several examinations of the ternary systems Na_2SO_4-$M''SO_4$-H_2O the solid phases have been identified merely from the appearance of the crystals. Schreinemakers's method of residues involving analyses of the moist solid phases is essential for deciding whether any variation in composition of the double salt occurs over the range of solutions with which it can be in equilibrium. Archibald and Gale (*J. Amer. Chem. Soc.*, 1924, **46**, 1760) made a complete examination of this nature of the system Na_2SO_4-$MgSO_4$-H_2O at 40° and 50°, and their results show that the double salt (astrakanite, $Na_2SO_4.MgSO_4.4H_2O$) has a fixed composition.

Benrath and Cremers (*Z. anorg. Chem.*, 1930, **189**, 86) examined the system Na_2SO_4–$ZnSO_4$–H_2O at 80° and found a fixed composition for the double salt $Na_2SO_4.ZnSO_4.4H_2O$. Benrath's figures for the corresponding nickel system (*ibid.*, 1931, **202**, 161) suggest that the composition of the double salt $Na_2SO_4.NiSO_4.4H_2O$ at 60° may be variable, while the only available data for the cobalt system (contained in the same paper) give two tie-lines for the system Na_2SO_4–$CoSO_4$–H_2O at 60°, which are inconclusive and intersect at some distance from the point for $Na_2SO_4.CoSO_4.4H_2O$.

We examined the system Na_2SO_4–$CoSO_4$–H_2O at 25°, using iron- and nickel-free cobalt sulphate, with all the usual precautions. Cobalt was weighed as Co_3O_4 after precipitation with 1-nitroso-2-naphthol; sulphate was determined by the standard method as $BaSO_4$; and the value for Na_2SO_4 was obtained by calculation. The results are given in the Table.

Solution.		Moist solid.		
$CoSO_4$, %.	Na_2SO_4, %.	$CoSO_4$, %.	Na_2SO_4, %.	Nature of solid.
—	21·80	—	—	$Na_2SO_4.10H_2O$
5·50	21·05	0·55	41·18	,,
9·66	20·13	0·86	42·13	,,
12·19	20·06	5·31	39·95	$Na_2SO_4.10H_2O$ and $Na_2SO_4.CoSO_4.4H_2O$
14·14	19·37	3·76	38·07	$Na_2SO_4.10H_2O$ (metastable)
13·25	18·68	35·53	33·25	$Na_2SO_4.CoSO_4.4H_2O$
13·80	17·98	36·22	34·15	,,
15·90	16·05	36·46	33·59	,,
19·70	12·85	38·83	34·58	,,
22·78	10·51	39·55	34·40	,,
23·30	10·68	37·72	32·05	,,
23·40	10·53	43·08	22·00	$Na_2SO_4.CoSO_4.4H_2O$ and $CoSO_4.7H_2O$
24·72	7·41	52·15	0·65	$CoSO_4.7H_2O$
25·90	4·39	52·78	0·64	,,
26·05	2·85	52·65	0·30 *	,,
27·33	—	—	—	,,

* Direct determination.

The lines for the double salt all run exactly to the point corresponding to $Na_2SO_4.CoSO_4.4H_2O$.

Caven and Gardener who had previously examined the cobalt system at 25° (*J.*, 1933, 943) made no analysis of solid phases. Their solubility curves agree well with ours, apart from the fact that their Na_2SO_4–double-salt point and the succeeding double-salt point appear to represent considerably supersaturated conditions. They give for the mixture point, $CoSO_4$, 15·29; Na_2SO_4, 19·40%.

We also re-examined the double-salt region of the 25° isotherm of the Na_2SO_4–$MgSO_4$–H_2O system and fully confirmed the results of Archibald and Gale (*loc. cit.*). We determined sodium by the zinc uranyl acetate method, as well as magnesium and sulphate, and the direct results for sodium agreed excellently with those calculated from the magnesium and sulphate determinations.

The new evidence for $Na_2SO_4.CoSO_4.4H_2O$, taken in conjunction with the results previously referred to for the corresponding magnesium and zinc salts, makes it highly probable that none of the double salts of this series has a variable composition.—The University, Reading. [*Received, March 29th*, 1950.]

The Reaction of Phenols with Phenyl and 1-*Naphthyl* iso*Cyanate.* By J. M. Lyons and R. H. Thomson.

The value of 1-naphthyl *iso*cyanate as a general reagent for the characterisation of phenols was first demonstrated by French and Wirtel (*J. Amer. Chem. Soc.*, 1926, **48**, 1736). These workers prepared some thirty 1-naphthylurethanes but they stated that polyhydric phenols, particularly catechol, resorcinol, quinol, and pyrogallol, did not react with 1-naphthyl *iso*cyanate. This is true only in the absence of a catalyst, since we find that reaction takes place readily in the presence of triethylamine (the catalyst which French and Wirtel recommended). The poly-1-naphthylurethanes have now been obtained by either heating the phenols with a slight excess of 1-naphthyl *iso*cyanate in boiling light petroleum (b. p. 100—120°) containing a drop of triethylamine for 20 minutes, or mixing the phenol and reagent in a dry test-tube and stirring with a glass rod previously dipped in triethylamine. The latter method is less suitable in most cases as the mixture usually solidifies so rapidly that effective stirring is not possible, and there is a tendency for *iso*cyanates to dimerise in contact with triethylamine. A number of new poly-1-naphthylurethanes and bisphenylurethanes are detailed below. Many of these derivatives are difficult to crystallise and some show unsatisfactory melting-points; in general they are not suitable for the characterisation of polyhydric phenols.

The failure of a number of monohydric phenols to form phenylurethanes is recorded in the literature. These include 2 : 6-diacetyl-3 : 5-dimethylphenol and various 4-substituted-2 : 6-di*tert.*-butylphenols (McKinley, Nickels, and Sidhu, *Ind. Eng. Chem. Anal.*, 1944, **16**, 304), 2 : 4-dinitrophenol, 4-chloro-2 : 6-dinitrophenol, and picric acid (Tarbell, Mallatt, and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 2229). The failure of juglone to react with phenyl *iso*cyanate has been reported by one of us (*J.*, 1950, 1737), and we now find that the *peri*hydroxyquinones, naphthazarin, 1 : 5- and 1 : 8-dihydroxyanthraquinone behave in the same way. This phenomenon has been attributed previously to the presence of negative groups, or to steric hindrance, but it may be observed that all the compounds mentioned above, with the exception of the 2 : 6-di-*tert.*-butylphenols, contain intra-molecular hydrogen bonds. It is well known that increasing acidity of the hydroxyl group, which would be promoted by the introduction of negative groups into the nucleus, increases the tendency to form hydrogen bonds, and this would explain why 2 : 4-dinitrophenol does not react with phenyl *iso*cyanate under any conditions whereas *o*-nitrophenol

does, although with difficulty (" Organic Reagents for Organic Analysis," Hopkin and Williams Ltd., London, 1944, p. 76; *cf.* McKinley *et al. (loc. cit.)*]. The reluctance of *o*-hydroxyazo-compounds to react with this reagent is also ascribed to hydrogen-bond formation (Hunter, *Ann. Reports*, 1946, **43**, 146) and it seems likely that the inability of some phenols to form urethanes is due in part to their hydrogen-bond structure, although steric considerations are obviously important in certain cases. However in such compounds as salicylaldehyde and methyl salicylate, the hydrogen bonds are not strong enough to suppress the normal reactivity of the hydroxyl group, and these compounds form phenylurethanes.

1-*Naphthylurethanes.*—*Catechol*, needles (from ethyl acetate), m. p. 174—175° (this compound melts and resolidifies immediately, finally decomposing at *ca.* 295°) (Found: C, 75·3; H, 4·5; N, 6·5. $C_{18}H_{20}O_4N_2$ requires C, 75·0; H, 4·5; N, 6·25%). *Resorcinol*, needles, m. p. 206° (from aqueous dioxan) (Found: C, 75·0; H, 4·5; N, 6·05%). *Quinol*, micro-crystals, m. p. 247°, from anisole (Found: C, 75·1; H, 4·7; N, 6·0%). *Pyrogallol*, micro-crystals (from glacial acetic acid), m. p. 181° (melts and resolidifies immediately, finally decomposing at *ca.* 270°) (Found: C, 74·0; H, 4·45; N, 6·3. $C_{39}H_{31}O_6N_3$ requires C, 73·9; H, 4·3; N, 6·6%). 1 : 4-*Dihydroxynaphthalene*, leaflets, m. p. 220° (from aqueous dioxan) (Found: C, 77·3; H, 4·7; N, 5·3. $C_{32}H_{26}O_4N_2$ requires C, 77·1; H, 4·45; N, 5·6%). 1 : 5-*Dihydroxynaphthalene*, needles, m. p. 240°, from aqueous dioxan (Found: C, 77·3; H, 4·6; N, 5·75%). 1 : 7-*Dihydroxynaphthalene*, micro-crystals, m. p. 185°, from aqueous acetic acid (Found: C, 77·3; H, 4·6; N, 5·8%). 1 : 8-*Dihydroxynaphthalene*, leaflets, m. p. 220°, from aqueous acetic acid (Found: C, 77·1; H, 4·7; N, 5·8%).

Phenylurethanes.—1 : 5-*Dihydroxynaphthalene*, leaflets (from glacial acetic acid), m. p. 225° (heated rapidly; when heated slowly it decomposes over a wide range) (Found: C, 72·5; H, 4·8; N, 6·8. $C_{24}H_{18}O_4N_2$ requires C, 72·35; H, 4·55; N, 7·0%). 1 : 7-*Dihydroxynaphthalene*, micro-crystals, m. p. 174°, from ethanol (Found: C, 72·05; H, 4·8; N, 6·9%). 1 : 8-*Dihydroxynaphthalene*, micro-needles (from glacial acetic acid), m. p. 229° (heated rapidly; decomposes gradually when heated slowly) (Found: C, 72·4; H, 4·3; N, 6·8%).

1 : 3-*Di*-1'-*naphthylureti*dione (1 : 3-*Di*-1'-*naphthyl*-1 : 3-*diaza*cyclo*buta*-2 : 4-*dione*).—One drop of triethylamine was added to 1-naphthyl *iso*cyanate (0·5 c.c.) and the mixture set aside in a stoppered tube. A few crystals rapidly appeared but three or four days elapsed before the whole mass solidified. Crystallisation from nitrobenzene and then from a large volume of boiling glacial acetic acid yielded colourless micro-needles, m. p. 295° (decomp. and sublimed) (Found: N, 8·3%. Calc. for $C_{22}H_{14}O_2N_2$: N, 8·3%). This corresponds to the compound obtained by Raiford and Freyermuth (*J. Org. Chem.*, 1943, **8**, 234) by the dimerisation of 1-naphthyl *iso*cyanate in the presence of triethylphosphine.

Analyses are by Miss M. A. B. Davie. One of us (J. M. L.) thanks the Carnegie Trust for the Universities of Scotland for a scholarship.—CHEMISTRY DEPARTMENT, MARISCHAL COLLEGE, ABERDEEN. [*Received, April 6th*, 1950.]

Pregn-5-ene-3β : *20β-diol*. By W. KLYNE and E. MILLER.

WIELAND and MIESCHER (*Helv. Chim. Acta*, 1949, **32**, 1922) described the preparation of pregn-5-ene-3β : 20β-diol by degradation of 3β-acetoxy-20-*iso*norchol-5-en-22-one with perbenzoic acid. We had previously prepared this diol by reduction of pregn-5-en-3β-ol-20-one with lithium aluminium hydride. Ott and Murray (Amer. Chem. Soc. 113th Meeting, *Abstracts*, 1948, p. 17K) stated that they had reduced pregnenolone with this reagent, but gave no details. The reduction of other steroid ketones by lithium aluminium hydride has recently been described by Shoppee and Summers (*J.*, 1950, 687: previous references there).

We have shown that our pregnenediol and its diacetate are identical with the compounds described by Wieland and Miescher, to whom we are most grateful for samples. The constitution of our diol was checked by its conversion into *allo*pregnane-3β : 20β-diol on catalytic hydrogenation.

20β-Hydroxy-steroids have usually been made from $C_{(20)}$-ketones in the past by catalytic hydrogenation (see, *e.g.*, Marker, Kamm, Jones, and Oakwood, *J. Amer. Chem. Soc.*, 1937, **59**, 614). Since this method is not suitable for the preparation of unsaturated 20β-hydroxy-compounds, lithium aluminium hydride may be useful as a general reagent for making such compounds.

Experimental.—(All m. p.s are corrected. Micro-analyses are by Drs. Weiler and Strauss, Oxford. All rotations were determined at 20—25° for the sodium D line in chloroform, by using a 0·5-dm. micro-tube. Samples for the determination of rotations were dried for 2 hours at 80° in high vacuum. Light petroleum is the fraction, b. p. 40—60°.)

Pregn-5-ene-3β : *20β-diol*. Pregn-5-en-3β-ol-20-one (240 mg., 0·76 millimol.; m. p. 185—187°) was dissolved in dry benzene (10 c.c.) to which dry ether (30 c.c.) was added. This solution was added dropwise to a solution in ether (15 c.c.) of lithium aluminium hydride (202 mg., 5·32 millimols.), and the mixture was refluxed gently for 30 minutes. The solution was cooled and a mixture of ether (10 c.c.) and acetone (2 c.c.) was added to decompose the excess of lithium aluminium hydride. More ether (50 c.c.) was added and the mixture was shaken with 2N-sulphuric acid (30 c.c.) to dissolve aluminium hydroxide. The aqueous solution was extracted with ether (50 c.c.), and the combined ethereal extracts were washed successively with 2N-sulphuric acid (10 c.c.), water (30 c.c.), 2N-sodium carbonate solution (10 c.c.), and water (3 × 10 c.c.), dried (Na_2SO_4), and evaporated to dryness. The product (229 mg.) crystallised from acetone (7 c.c.) in rosettes of needles, m. p. 196—199° (124 mg.). Concentration of the mother-liquors afforded 40 mg. of similar material (total yield, 68%). This material on crystallisation from light petroleum–ethyl acetate gave silky needles, m. p. 201·5—203·5°, which contained one molecule of acetone of crystallisation (Found: C, 76·1; H, 10·7. Calc. for $C_{21}H_{34}O_2.C_3H_6O$: C, 76·5; H, 10·7. Calc. for $C_{21}H_{34}O_2$: C, 79·2; H, 10·8%). Crystallisation from methanol gave thick needles, m. p. 199—200°, which apparently contained half a molecule of methanol of crystallisation; mixed m. p. (with sample supplied by Wieland and Miescher) 200—202°: $[\alpha]_D$ −65·3° ± 1·7° (*c*, 0·77), ($[\alpha]_D$ −68·5°, calculated for substance without methanol of crystallisation); $[M]_D$ −218° (Found: C, 77·3; H, 10·7. Calc. for

$C_{21}H_{34}O_2,\frac{1}{2}CH_4O$: C, 77·2; H, 10·8%). Wieland and Miescher (*loc. cit.*) give m. p. 200·5—201·5°; $[\alpha]_D$ −64° ± 3°. The tetranitromethane test for unsaturation was positive; the Zimmermann keto-steroid reaction was negative.

Wieland and Miescher obtained the diol without solvent of crystallisation by sublimation at 150° in high vacuum. We were unable to repeat this; two samples sublimed at 160° and 5 × 10^{-4} mm. pressure gave analytical figures for carbon about 1% lower than those calculated for the unsaturated diol (Found: C, 77·9, 78·2; H, 10·6, 10·4. Calc. for $C_{21}H_{34}O_2$: C, 79·2; H, 10·8%).

Pregn-5-ene-3β: *20β-diol diacetate*. The pregnenediol was acetylated by heating it with acetic anhydride at 100° for 2 hours. The product was chromatographed on alumina (B. D. H.) and after three crystallisations from methanol containing 20% of water formed needles, m. p. 130—131°, $[\alpha]_D$ −36·6° ± 1·0° (*c*, 0·94); $[M]_D$ −147° (Found, on a sample sublimed at 160°/5 × 10^{-4} mm.: C, 74·1; H, 9·5%. Calc. for $C_{25}H_{38}O_4$: C, 74·6, H, 9·5%). Mixed m. p. (with sample supplied by Wieland and Miescher) 127—128°. These authors (*loc. cit.*) give m. p. 125—126°; $[\alpha]_D$ −39° ± 2°.

Hydrogenation of pregn-5-ene-3β: *20β-diol*. The pregnenediol (36 mg.) was hydrogenated in the presence of Adams's platinum oxide catalyst (20 mg.) in glacial acetic acid (20 c.c.). The product, *allo*pregnane-3β: 20β-diol, crystallised from light petroleum–ethyl acetate in rosettes of leaflets, m. p. 194·5—195·5°; $[\alpha]_D$ +4·4° ± 1·0° (*c*, 1·04); $[M]_D$ +14° (Marker, Kamm, Jones, and Oakwood, *loc. cit.*, give m. p. 195—196°). Authentic *allo*pregnane-3β: 20β-diol, prepared by hydrolysis of the 3-acetate (Klyne and Barton, *J. Amer. Chem. Soc.*, 1949, **71**, 1509), had m. p. 194—195°, $[\alpha]_D$ +2·9° ± 0·9° (*c*, 1·02): $[M]_D$ +9°. Mixed m. p. with the product of hydrogenation 195—196°.

The *allo*pregnanediol obtained by hydrogenation was acetylated by heating it with acetic anhydride. The diacetate after crystallisation from light petroleum–ethyl acetate formed long needles, m. p. 141—142·5°; mixed m. p. 140—142° with authentic material (m. p. 140·5—142°, Klyne and Barton, *loc. cit.*).

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Postgraduate Medical School, Ducane Road, London, W.12. [*Received, April 11th*, 1950.]

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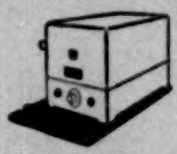

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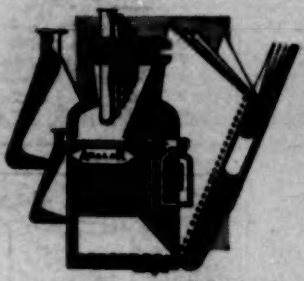

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